Commentary

Antifibrotics in India

Raja Dhar

Department of Pulmonology, Fortis Hospital, Kolkata, West Bengal, India
E-mail: docaardee@yahoo.com

Antifibrotics have become established as an established mode of therapy in patients with idiopathic pulmonary fibrosis (IPF). The two agents in current use are pirfenidone and nintedanib. Pirfenidone inhibits transforming growth factor-beta and tumor necrosis factor-alpha.[1,2] The ASCEND and the CAPACITY trials established that the drug reduced the risk of disease progression and 1-year mortality by ~50%.[3,4] Nintedanib, on the other hand, is a tyrosine kinase inhibitor. The INPULSIS trials show that this drug slows disease progression by reducing annual forced vital capacity (FVC) decline by ~50%.[5] There is also a numerical reduction in the risk of acute exacerbations and a numerical reduction in all-cause mortality.

While both of the agents are used by pulmonologists all over the globe including India, published data about the experience of pulmonary physicians regarding their use are scant. The current issue of Lung India carries the Indian experience on the use of the antifibrotic nintedanib coming from Hinduja Hospital in Mumbai.[6] It made me introspect on where we were placed based on the current evidence as far as the use of antifibrotics is concerned.

A problem arises regarding which one is superior and which to choose first. There are no head-to-head trials to establish this. However, there have been efforts to phenotype patients even within the cohort of patients with IPF. The INPULSIS trials showed that the drug worked well in patients with probable usual interstitial pneumonia (UIP) pattern on computed tomography (UIP pattern without honeycombing) and combined pulmonary fibrosis and emphysema.[5] Hence, maybe nintedanib could be used as a first line in these phenotypes of patients.

The limiting factor with nintedanib in countries like India which depends mainly on private health care and low health insurance rates is the high cost of this drug. Hence, in a lot of patients, the choice between the two available antifibrotics is determined by what the pocket permits rather than evidence-based indications.

This sometimes makes nintedanib an "automatic second choice" for a lot of clinicians and gets prescribed after pirfenidone has been tried. This usually means prescribing Nintedanib when the FVC has declined significantly. Hence, the current study from Hinduja also has a borderline mean FVC of around 50%. It would be presumed that some of the patients in this study had FVC <50%. This raises the question regarding whether this drug works in FVC <50%? The RECAP study showed a similar decline in patients with FVC <50% (annual rate of decline: 2.1%) compared to patients with FVC >50% (annual rate of decline: 2.7%) independent of previous therapy.[7]

What do you do if the FVC declines >10% after 1 year of treatment with pirfenidone? Studies have shown that continued use of Pirfenidone in Year 2 after the FEV1 has declined by more than 10% in Year 1, might still slow down the decline of FVC in the second year.[8] Hence, if there is a natural rapid disease progression without exacerbations, one might give the patient the option to continue pirfenidone. However, if there is one or more exacerbations in a given year, it might be prudent to change to nintedanib.

This is also based on the systematic review and meta-analysis published by Rogliani *et al*. on indirect treatment comparisons of pirfenidone, nintedanib, and N-acetylcysteine (NAC).[9] Results showed that both pirfenidone and nintedanib, but not NAC, were significantly effective in reducing FVC decline over 12 months. Nintedanib significantly protected against the risk of acute exacerbation and mortality. Pirfenidone and nintedanib showed a similar and good safety profile, whereas NAC provided a signal for increased adverse events.

Some patients become psychologically overwhelmed by the number of tablets they need to take for pirfenidone and hence cut down on the dose. This leads to subtherapeutic dosing and hence less clinical efficacy.[10] This is something that needs to be taken into account when choosing an antifibrotic for an individual patient, especially in countries like India where the drug comes only as 200 mg tablet.

In my experience, the side effect profile of both the drugs seems to be reasonably favorable in the Indian population. This might be because the Indian patients are more tolerant than their Western counterparts, especially for a disease where they feel this might be their last hope for long-term survival.

Reduction of dose of nintedanib – We did a small survey looking at the incidence of diarrhea in 7 centers and

across 32 patients in these centers. Significant diarrhea necessitating reduction of dose (four patients) or stoppage of drug (two patients) happened in only 18.75% of patients (unpublished data). Hence, again, diarrhea seems a lesser evil in retrospective Indian data compared to what was found in the INPULSIS trial.

The scope of antifibrotics is expanding beyond IPF. Studies such as SENSCIS (systemic sclerosis-associated interstitial lung disease [ILD]) with nintedanib,[11] RA-ILD Lung Study[12] (TRIAL 1) with pirfenidone, and EPOS Study with pirfenidone for bronchiolitis obliterans[13] and pirfenidone for non-IPF ILD[14] are all near completion. The nomenclature PF-ILD includes a variety of diagnosis for non-IPF ILD where there are traction bronchiectasis and honeycombing,[15] and hence, in theory, antifibrotics should work.

This is a positive trend for a country like India where the incidence of IPF seems much lower than the West. The ILD India Registry highlighted that about 47% of patients with ILD had chronic hypersensitivity.[16] Pirfenidone has been tried in real-life studies from Japan for this condition with reduction in the decline of FVC.[17]

The next question which would arise would be the place of a combination of pirfenidone and nintedanib in the treatment of fibrotic lung disease. The combination regimen has been found to be safe and tolerable in Phase II trials.[18] Efficacy trials (Phase III) are still awaited.

Hence, in conclusion, with the expanding indication for the use of antifibrotics, we need greater clarity regarding which drug to choose in various conditions and their phenotypes. This can only happen when we have head-to-head trials for efficacy.

REFERENCES

1. Conte E, Gili E, Fagone E, Fruciano M, Iemmolo M, Vancheri C. Effect of pirfenidone on proliferation, TGF-β-induced myofibroblast differentiation and fibrogenic activity of primary human lung fibroblasts. Eur J Pharm Sci 2014;58:13-9.
2. Nakazato H, Oku H, Yamane S, Tsuruta Y, Suzuki R. A novel anti-fibrotic agent pirfenidone suppresses tumor necrosis factor-alpha at the translational level. Eur J Pharmacol 2002;446:177-85.
3. King TE Jr., Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, *et al*. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2083-92.
4. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, *et al*. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): Two randomised trials. Lancet 2011;377:1760-9.
5. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, *et al*. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071-82.
6. Mullerpattan JB, Porwal SH, Sarkar TA, Wagh HD, Udwadia ZF. Use of nintedanib in patients with idiopathic pulmonary fibrosis: Initial Indian experience. Lung India 2019;36:465-6.
7. Costabel U, Albera C, Kirchgaessler KU, Gilberg F, Petzinger U, Noble P. Analysis of patients with idiopathic pulmonary fibrosis (IPF) with percent predicted forced vital capacity (FVC)‹50% treated with pirfenidone (PFD) in RECAP. Eur Respir J 2016;48 Suppl 60:OA1813.
8. Nathan SD, Albera C, Bradford WZ, Costabel U, du Bois RM, Fagan EA, *et al*. Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: Analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis. Thorax 2016;71:429-35.
9. Rogliani P, Calzetta L, Cavalli F, Matera MG, Cazzola M. Pirfenidone, nintedanib and N-acetylcysteine for the treatment of idiopathic pulmonary fibrosis: A systematic review and meta-analysis. Pulm Pharmacol Ther 2016;40:95-103.
10. Dhar R, Satish KS, Rajan S, Vijai Kumar R, Udwadia Z, Dumra H, *et al*. Clinical profile and early follow-up of patients receiving pirfenidone in the PIONEER observational study. Eur Respir J 2014;44 Suppl 58:P3792.
11. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, *et al*. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med 2019;380:2518-28.
12. Rosas IO. Phase II Study of Pirfenidone in Patients With RAILD (TRAIL1); 04 July, 2019. Available from: https://clinicaltrials.gov/ct2/show/record/NCT02808871. [Last accessed on 2019 Aug 06].
13. Perch M. European Trial of Pirfenidone in BOS, a European Multi-Center Study (EPOS); 31 August, 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT02262299. [Last accessed on 2019 Aug 06].
14. Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M, *et al*. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: Design of a double-blind, randomised, placebo-controlled phase II trial. BMJ Open Respir Res 2018;5:e000289.
15. Cottin V, Hirani NA, Hotchkin DL, Nambiar AM, Ogura T, Otaola M, *et al*. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. Eur Respir Rev 2018;27. pii: 180076.
16. Singh S, Collins BF, Sharma BB, Joshi JM, Talwar D, Katiyar S, *et al*. Interstitial lung disease in India. Results of a prospective registry. Am J Respir Crit Care Med 2017;195:801-13.
17. Shibata S, Furusawa H, Inase N. Pirfenidone in chronic hypersensitivity pneumonitis: A real-life experience. Sarcoidosis Vasc Diffuse Lung Dis 2018;35:139-42. [Internet]. Available from: http://www.mattioli1885journals.com/index.php/sarcoidosis/article/view/6170. [Last cited on 2019 Aug 19].
18. Vancheri C, Kreuter M, Richeldi L, Ryerson CJ, Valeyre D, Grutters JC, *et al*. Nintedanib with add-on pirfenidone in idiopathic pulmonary fibrosis. Results of the INJOURNEY trial. Am J Respir Crit Care Med 2018;197:356-63.

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/lungindia.lungindia_379_19

How to cite this article: Dhar R. Antifibrotics in India. Lung India 2019;36:445-6.