Editorial

Is pirfenidone ready for use in non-idiopathic pulmonary fibrosis interstitial lung diseases?

Pirfenidone is an orally active drug with anti-inflammatory and anti-fibrotic actions.[1] In this issue of the journal, Udwadia *et al*. report the successful treatment of connective tissue disease (CTD)-associated interstitial lung disease (ILD), with pirfenidone, in a patient with systemic sclerosis (SSc).[2] The index patient was a 44-year-old lady with SSc-ILD, diagnosed on high-resolution computed tomography of the chest, showing a pattern of fibrotic nonspecific interstitial pneumonia (NSIP). She had worsening dyspnea and declining lung function despite immunosuppression with corticosteroids, cyclophosphamide, and azathioprine. Treatment with 600 mg/day of pirfenidone (started as compassionate use) for 20 months, led to supposed improvement in the symptoms, lung function, diffusion capacity for carbon monoxide, and arterial oxygen saturation.

Pirfenidone is recommended for use in patients with idiopathic pulmonary fibrosis (IPF), with a moderate restrictive defect on spirometry (forced vital capacity between 50 and 80% predicted).[3]Although, first tried in IPF on a compassionate basis in an open-label study,[4] it was the phase II and phase III Japanese trials, the two CAPACITY trials and the more recent ASCEND trial that brought in scientifically sound evidence to support the fact that this drug slows down the decline of lung function in IPF.[5-8] The drug is now being studied in animal models for non-IPF ILDs and non-pulmonary fibrotic conditions.[9-12] It has also been evaluated in humans with non-pulmonary fibrosing disorders.[13,14] Its efficacy in SSc-ILD has been previously reported, although the study has included only five patients.[15] The question is whether pirfenidone is actually effective in non-IPF ILDs?

The pathogenesis of IPF involves alveolar epithelial cell damage, which leads to production of several growth factors by these activated epithelial cells, which include transforming growth factor (TGF)-β, platelet derived growth factor (PDGF), fibroblast growth factor (FGF), and tumor necrosis factor (TNF)-α.[1] This initiates the migration and proliferation of fibroblasts. As appropriate repair of the damaged epithelium fails to occur, a dysregulated wound healing process results, further establishing a persistent fibroproliferative state. Pirfenidone acts by regulating TGF-β, thus slowing down the fibrotic process. As TGF-β is also a key cytokine in SSc-ILD, it seems biologically plausible that the drug may be effective in this disease,[16] or for that matter, it is possible that the drug may act in any fibrotic ILD in which TGF-β plays a major role. However, currently all these are hypothetical statements and evidence to support this theory needs to be generated.

In the case reported by Udwadia *et al*., the ILD was not advanced on imaging (in contrast to the results of spirometry) and the dose of pirfenidone used was only 600 mg/day. Hence, the possibility of spontaneous stabilization of the disease cannot be excluded. Another important possibility is that the progression of ILD was a result of drug-induced toxicity (both cyclophosphamide and azathioprine are known to cause ILD) and it remitted when these medications were withdrawn.[17,18] Although apparent efficacy of a lower dose of the drug in the index patient may be attributed to the lower body weight of Indian patients or to the racial, ethnic, and geographical differences in the pharmacokinetics of the drug, this requires further investigation. The dose of pirfenidone used in the Japanese phase III trial was 1800 mg per day, while in the CAPACITY 004 trial it was 1197 mg/day and 2403 mg/day.[6,7] It was observed that even the 1197 mg/day dose was less effective than the 2403 mg/day dose. A weight-based dosing regimen (using 40 mg/kg/day) of pirfenidone has also been suggested.[19]

The beneficial effect noted in the case report does not mean that pulmonologists should start using pirfenidone in non-IPF ILDs. In our opinion, at present, pirfenidone must not be used in cellular NSIP, cryptogenic organizing pneumonia, and other ILDs, where there is preponderant cellular inflammation; the mainstay of treatment in such situations should be steroids or immunosuppressive agents. There is, however, an urgent need to evaluate the efficacy of pirfenidone in the fibrotic NSIP pattern and the fibrotic stage of other ILDs. The most common cause of death in patients with systemic sclerosis is ILD.[20] If pirfenidone proves to be effective, it will be a boon for patients with this sclerosing disorder, which perplexes the rheumatologists and the pulmonologists alike. The report brings out the important need for a systematic assessment of the efficacy of pirfenidone in SSc-ILD, as well as in other non-IPF ILDs by means of properly conducted randomized controlled trials. This would ensure that we do not deny

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our patients an effective option in fibrotic ILDs that are resistant to immunosuppression.

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