

## Editorial

## Revealing Real-Life Experiences With Antifibrotic Drugs in Idiopathic Pulmonary Fibrosis



### Experiencias de vida real con fármacos antifibróticos en la fibrosis pulmonar idiopática

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Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and usually lethal fibrosing interstitial pneumonia of unknown cause.<sup>1</sup> IPF is an aging associated-disease, limited to the lungs, and characterized by the histopathologic and/or radiologic pattern of usual interstitial pneumonia.<sup>2</sup> During many decades the disease was considered a chronic inflammatory disorder, and accordingly, IPF patients were treated with corticosteroids and immunosuppressive drugs without modifications in its natural history, and often with accelerated deterioration of the clinical course.<sup>3</sup> In addition, numerous clinical trials with potential therapies for IPF were performed without success.<sup>4</sup> In the last years accumulating evidence demonstrate that IPF is provoked by aberrantly activated lung epithelial cells which secrete numerous mediators, leading to the expansion of the fibroblasts/myofibroblasts population and ultimately to the excessive accumulation of extracellular matrix with destruction of the lung architecture.<sup>5</sup> This change of paradigm framework led to changes in the search of antifibrotic drugs, and in 2014 two large phase-III clinical trials provided robust evidence that pirfenidone and nintedanib slowed the rate of functional decline and consequently were approved by the regulatory agencies around the world.

ASCEND trial was a phase-III randomized placebo-controlled study, that demonstrated that the use of pirfenidone resulted in a marked reduction of the decrease of forced vital capacity (FVC) with acceptable safety and tolerability profile.<sup>6</sup> Pirfenidone is a synthetic compound with putative anti-fibrotic, anti-inflammatory, and antioxidant activities including the inhibition of transforming growth factor-beta (TGF- $\beta$ ), a strong inductor of fibrosis.<sup>7</sup>

INPULSIS trials were two replicates, randomized, placebo-controlled phase-III trials that showed a positive effect of nintedanib on the reduction of the annual rate of decline in FVC, and also exhibited significant benefits on key secondary endpoints such as the time to the first acute exacerbation. The most frequent adverse event was diarrhea, but was generally well tolerated.<sup>8</sup>

Nintedanib inhibits several tyrosine kinases interfering with a number of pathogenic processes that have been implicated in the biopathology of IPF, including fibroblast proliferation, migration and activation.<sup>9</sup>

However, these clinical trials have important limitations, primarily the follow-up time because all of them were done at 52 weeks, and the inclusion criterions that allowed only the enrollment of IPF patients with mild or moderate disease. In this context, it is already unclear whether these drugs will slow the disease process for longer periods of time with tolerable adverse effects. Furthermore, it is uncertain whether the positive effects of these drugs will also be observed in IPF patients with severe functional impairment and/or known comorbidities.

In the absence of long-term clinical trials, "real-life" experiences may give some light and several of them have been recently published. For example, an Italian study reported that pirfenidone reduced the rate of annual FVC decline even in severe IPF, suggesting that the treatment was useful in advanced disease.<sup>10</sup> By contrast, in a study performed in Germany, the effect of pirfenidone on lung function decline after the start of treatment with pirfenidone compared to the pretreatment period was not significant.<sup>11</sup> Regarding nintedanib, a nationwide multicenter experience also performed in Italy that included patients with severe IPF showed that nintedanib slows down the rate of decline of DLCO but does not have significant impact on FVC or another lung parameters.<sup>12</sup> In general, however, all these studies have been retrospective and observational.

In this issue of the journal, Dr. Caro and coworkers (Caro FM, et al. Experiencia de la vida real con pirfenidona en la fibrosis pulmonar idiopática en Argentina. Estudio retrospectivo multicéntrico. Arch Bronconeumol. 2017 (<https://doi.org/10.1016/j.arbres.2018.06.014>) report a study designed to evaluate the security of pirfenidone in 50 patients of four Argentine's centers specialized in interstitial lung diseases. This was also a retrospective, observational study, covering from June 2013 to September 2016 with an average of days in treatment of 645 days. Twenty-six patients were followed up for 1 year and 14 patients for 2 years. When they compared the periods pre-pirfenidone and post-pirfenidone found that the declination of FVC was 4% versus 2%

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respectively. However, the analysis according to the severity of the disease showed a tendency to improvement in the subgroup of patients with FVC  $\geq$  75%, with change in the median of 1% versus -5% ( $p=0.09$ ) emphasizing the importance of early diagnosis and start of anti-fibrosis treatment. Importantly, no differences were found in the presence of emphysema in both groups.

In the period of study, they reported 19 adverse events in 15 patients (30%) consisting mainly in gastrointestinal effects. From them, 36% suspended the treatment during the study but only 3% definitively which is lower to other reported real-life studies. Thirteen patients died, all of them by causes related with IPF, 38.5% by acute exacerbation and 61.5% by disease progression. There was the same proportion of adverse effects in patients with IPF alone or combined with emphysema. Of principal interest is that significant higher mortality was observed in the group that suspend the treatment, which was mainly caused by problems with insurance companies, a frequent problem in developing countries where the access to insurance is limited and many patients cannot pay the high cost of the drug.

The principal limitation of this study is a problem well identified in our countries, that is the loss of follow up due to the extensive territorial surface and poverty, which make very difficult for the patients to move from their cities to the place where is localized the specialized center. In this study only 56% of the population had functional follow up, and this made it difficult to evaluate the efficacy of pirfenidone in the time.

The conclusion of this study performed in Argentina, is that similarly to others real-life studies, pirfenidone had good tolerance, but the long-term functional efficacy is unclear.

Although the real-life studies performed in IPF are helping us to know the safety of antifibrotic drugs for prolonged periods, they are not serving to determine the long-time clinical/functional efficiency of the drugs. Long-term prospective clinical trials including

IPF patients with severe disease are necessary to find out whether pirfenidone or nintedanib may improve survival and quality of life for extended periods of time and perhaps to identify biomarkers as predictors of response.

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