EDITORIAL

Using evidence in clinical practice: A dream coming true in idiopathic pulmonary fibrosis

The large, pivotal phase 3 randomized clinical trials (RCT) of pirfenidone and nintedanib (ASCEND and INPULSIS)\(^1,2\) revolutionized the pharmaceutical landscape of idiopathic pulmonary fibrosis (IPF), leading to the approval of the first two agents capable of modifying the disease course. Nevertheless, as in many other areas of medicine, the years following such landmark achievement proved that translating evidence from RCT in daily clinical practice is far from straightforward. The results of these trials could not fully address the issue of the considerable, still unrumled heterogeneity of disease course: because of their design, RCT do not provide guidance regarding efficacy and safety of drugs at the level of single individual. Furthermore, the lack of comparative trials of the two drugs in the same population of IPF patients does not allow physicians and patients to make an informed decision as to which compound might be most beneficial in the individual patient, thus leaving the choice of the first-line therapy to the personal judgment of the physician. This decision is usually made solely upon the side effect profile of the drugs, or taking into consideration other factors such as patient’s personal preferences, or financial issues in some countries.

Indeed, rigorous post-hoc analyses of pooled data from both ASCEND and INPULSIS trials, extension studies and a few isolated real-life experiences have recently provided some important hints about the practical use of these two drugs.\(^3\)\(^-\)\(^9\) These clinically relevant findings are accurately described by Carlos Robalo-Cordeiro and his co-workers in a Special Article published in the Portuguese Journal of Pulmonology.\(^10\) Several relevant topics are addressed in this exhaustive article. With regard to the timing for treatment initiation in those patients presenting at an early stage of their disease, the advantages of starting treatment for preventing or slowing down future functional deterioration seem to prevail over a "wait and see" approach. The available evidence of similar decline and response to treatments in patients with preserved lung function as compared to patients with functional impairment further supports the clinical relevance of setting an earlier confident diagnosis of IPF. Nevertheless, the feasibility of screening programs dedicated to IPF detection is currently ruled out by the relative low prevalence of the disease in the general population and the costs and radiation risks related to the key diagnostic test, chest high-resolution computed tomography (HRCT). Most importantly, it would raise concerns of the potential detection of asymptomatic cases with nonspecific interstitial radiological abnormalities, most of whom would probably not clinically progress over time. On the other hand, the identification of a reliable molecular signature of an "early IPF" phenotype could help identify a population that might benefit from treatment at the earliest signs of interstitial involvement. Recent advances in genetic sequencing and bioinformatics have made it easier to detect genetic variants rapidly, however the biological effect over time of those genetic signatures is largely unknown, and so is the influence of environmental factors (such as epigenetic factors, or the largely discussed lung microbiome) on such variants toward the development of a progressive fibrosis.\(^11\)

Large population sequencing studies are currently under way and the results are awaited to allow deeper understanding of the penetrance and effect sizes of common and rare genetic variants with regard to distinct clinical phenotypes.

On the other end of the spectrum of the IPF population, the benefits of starting treatment in patients with advanced disease remains unknown. The few, currently available data from open-label extension studies seem to suggest that this population with more severe functional impairment might also benefit from treatment, but more robust evidence is required in order to produce a shift of perspective in many regulatory agencies, most of which narrowed the indication to treat the mild to moderate IPF population included in the RCT. Indeed, it does not seem convenient to interrupt either anti-fibrotic treatment as long as tolerability is not an issue, as both pirfenidone and nintedanib seem to maintain efficacy over several years, even when disease progression is evident. As a matter of fact, this might represent indirect
evidence in support of commencing treatment irrespective of the severity of lung function impairment at baseline. Since the lack – or loss – of efficacy can only be presumed in the individual patient, the strategy of switching from one agent to the other should be reserved for those cases where first line therapy is not tolerated. In stark contrast, the addition of a second drug is a foreseeable scenario in patients who do not present significant side effects related to the initial treatment. To date though, the only available data on the combination of pirfenidone and nintedanib come from a single centre study with 50 participants and is highly inconclusive as to tolerability and pharmacokinetics of the two drugs administered together.13 Although more data on the safety of a combined approach with both drugs should become available soon, the formal demonstration of the superior effectiveness of the combined therapy will not be straightforward either. The pleiotropic, diverse actions of the two agents suggest good probability of an additive (if not synergistic) effect, albeit the comparison of the combination regimen with monotherapy will hurdle the design of future trials, requiring larger population size and longer duration to ensure adequate statistical power.

In conclusion, pirfenidone and nintedanib represent two safe and effective, alternative (at the moment) therapeutic options to be offered to patients with a confident diagnosis of IPF and mild to moderate disease severity. However, in the era of precision medicine, the pharmacologic scenario of IPF still looks in its sophomore year. Novel agents with more targeted actions are going to surface over the next few years and combination therapy will hopefully soon become a standard of care in IPF. The adoption of effective disease stratification strategies in RCT via the validation of predictive biological markers will be therefore required to ensure a personalized approach is achieved in IPF.

References