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Pharmacological treatment of idiopathic pulmonary fibrosis: time to step out of the comfort zone?

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Over the last two decades, the efforts made by international respiratory societies worldwide to standardize diagnostic criteria of idiopathic pulmonary fibrosis (IPF) crucially enabled a deeper understanding of the pathogenetic mechanisms of the disease, thus leading to outstanding therapeutic achievements. After many years of disappointing trials, nintedanib and pirfenidone ultimately emerged as the first effective drugs in slowing down the rate of decline in lung function in these patients,[1,2] heralding the dawn of a new era in the management of IPF. The approval of the two drugs by regulatory agencies—pirfenidone received approval for use in Japan in 2008, in Europe in 2011, and in the USA in 2014, whereas nintedanib received approval for use in the USA in 2014 and in Europe in 2015—sanctioned the widespread use of antifibrotic treatment for IPF in clinical practice. The increasing amount of evidence from well-designed randomized clinical trials in the first half of the last decade warranted an update of the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) evidence-based guidelines[3] for the management of IPF patients, which provided an unprecedented conditional recommendation in favor of the pharmacological treatment with either pirfenidone or nintedanib. Over the last years, further proof of safety and efficacy in the long term of both agents has been delivered by open-label extension studies and various real-life experiences.

In this issue of the *Jornal Brasileiro de Pneumologia*, the working group led by Baddini-Martinez provides a pragmatic, evidence-based set of recommendations for guiding the use of pharmacological therapies in IPF patients in Brazil.[4] The panel of experts focused on Patients of interest, Intervention to be studied, Comparison of intervention and Outcome of interest (PICO)-style questions related to seven types of treatment for IPF. According to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, clinical outcomes (stratified as critical, important, and unimportant) and quality of available evidence were the major factors considered to express conditional or strong recommendations in favor of or against the investigated types of treatment. A peculiar methodological feature of these guidelines is represented by the search strategy: the choice to evaluate systematic reviews with meta-analyses instead of single studies facilitated a synthetic reporting of outcomes and allowed, up to a certain extent, indirect comparisons of treatments to be made. Unsurprisingly, the group of experts confirmed a conditional recommendation in favor of pirfenidone and nintedanib, which were found to be similarly effective in reducing the risk of occurrence of a > 10% decline in FVC as compared with placebo (estimated OR = 0.64 and 0.61, respectively). The use of anticoagulant therapy was strongly discouraged, corroborating the ATS/ERS/JRS/ALAT guidelines.[3] Likewise, phosphodiesterase-5 inhibitors received a conditional recommendation against use; importantly, the authors note that the combination of sildenafil with nintedanib also failed to prove greater benefit when compared with the use of nintedanib alone in a recent trial,[5] although that study could not be included in the current statement because it was published after the completion of the analyses for the present guidelines.[4] A small, although noteworthy, divergence from the 2015 ATS/ERS/JRS/ALAT guidelines[3] regards the recommendation on the use of antacids in IPF: the international guidelines[3] expressed a conditional recommendation for antacid treatment in all patients with IPF, whereas the present Brazilian guidelines[4] were unable to find articles suitable for developing recommendations for or against the pharmacological treatment of gastroesophageal reflux because of the low quality of the available evidence, mostly consisting of retrospective observational studies. The position taken by the Brazilian working group[4] finds support in a recent methodological study[6] showing how the findings of various studies on the impact of anti-reflux treatment in IPF are substantially biased by the time required to define treatment exposure, which inherently determines a survival advantage.

In conclusion, the Brazilian Thoracic Association statement not only represents a useful, practical guide for Brazilian physicians to approach IPF patients, but it also provides the most up-to-date standpoint on the use of pharmacological therapies that have been evaluated in the treatment of IPF over the last two decades. Now that the benefits of pirfenidone and nintedanib in IPF have been long proven, the scientific community will be soon called to pronounce on new emerging questions. Recent studies have provided compelling evidence of efficacy of current antifibrotic medications in other forms of interstitial lung diseases[7-9]; for example, in the future, starting antifibrotic therapy is likely to be extended to patients showing signs of disease progression irrespective of its etiology and classification. In this scenario, the identification of criteria indicating clinically meaningful disease progression will be critical to guarantee a timely and appropriate start of treatment, properly balanced by the risks related to potential adverse effects. Most importantly, the search

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for novel effective agents to halt IPF progression has brought to the first positive phase 2 trials in years[10-12]: hopefully, the next era of pharmacological treatment of IPF will offer the opportunity to combine different drugs in a more patient-tailored approach. So far, the approach of combining the two approved therapies for IPF has been surrounded by many uncertainties, and although a few open-label studies showed the lack of significant interaction between the two drugs and the relative safety of combined therapy, to date, there is insufficient evidence for respiratory societies or regulatory agencies to endorse it. Building on the design of many recent and ongoing IPF randomized trials that will allow for background therapy, the approach of associating a targeted, highly tolerable novel therapy on top of currently antifibrotic drugs might become more appealing and outclass the urgency to further prove the synergistic effect of the coadministration of nintedanib and pirfenidone.

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