Arch Bronconeumol. 2018;54(1):1–2

Sociedad Española de Neumología y Cirugía Torácica SEPAR

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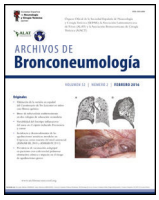

Editorial

What's New in Idiopathic Pulmonary Fibrosis?☆

Qué hay de nuevo en la fibrosis pulmonar idiopática

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The interest of the scientific community in idiopathic pulmonary fibrosis (IPF) has increased exponentially in recent years, as demonstrated by the sheer volume of recent publications on the diagnosis, biomarkers, prognosis, and treatment of this disease. The approval of pirfenidone and nintedanib and the wider use of these treatments, which have been shown to be effective and safe in patients with IPF, now compels clinicians to make a greater effort to diagnose this condition as early and as accurately as possible.

In the early diagnosis of IPF, cases of subclinical interstitial lung disease (ILD) have been detected in individuals included in low-dose computed tomography lung cancer screening programs, raising questions regarding their future progress and whether a lung biopsy should be performed to confirm the diagnosis. Perhaps the best approach in this event is to monitor patients with a higher risk of developing pulmonary fibrosis (*e.g.*, those with a family history of IPF, connective tissue disease, smokers), possibly in the future with a combination of radiological findings and certain biomarkers, such as polymorphisms in the mucin 5 B promoter region and serum levels of metalloproteinase 7.[1]

As regards clinical evaluation, the importance of pulmonary auscultation, even in this technological age, has been underlined in a study by Sellarés et al.[2] who found that the auscultation of Velcro crackles in patients with suspected ILD was associated with a radiological pattern of usual interstitial pneumonia (UIP). The authors urge primary care physicians to be aware of the importance of an early diagnosis of DILD in their setting.

At a time in which clinical guidelines recommend improving diagnostic accuracy with a multidisciplinary assessment by pulmonologists, radiologists, and pathologists with experience in the diagnosis and management of ILD, up to 10% of patients with chronic fibrosing diseases are still diagnosed as unclassifiable, even in expert centers. New diagnostic procedures, such as transbronchial cryobiopsy, are attracting attention and becoming a very active area of research. In a recent study of 117 patients with fibrotic ILD,[3] cryobiopsy was shown to be safe and effective for obtaining useful lung tissue samples, and this technique will probably be incorporated into diagnostic algorithms for IPF in the near future. A recent review of the role of LDCT in IPF proposes[4] a modification of some of the radiological criteria of UIP, such as the need for a honeycomb pattern, and the incorporation of heterogeneity as a secondary criterion, but changes have not yet been implemented in the clinical guidelines.

New imaging technologies are being developed, including diagnostic tools such as micro-CT, an imaging technique that may bridge the gap between the currently available thin-section CT and histology,[5] and computerized algorithms.[6] In the immediate future, these techniques may help radiologists achieve greater diagnostic and prognostic accuracy.

Precision personalized medicine will be the next great advance in IPF.[7] The complexity of the different pathogenic pathways involved in the genesis of IPF is illustrated by the number of molecular and genetic biomarkers[8] under investigation, several of which are being validated in longitudinal studies and may be available in the near future. Some patient subgroups, characterized by differences in genetics, molecular pathways, environmental factors, and lifestyle, have already been defined. Certain genetic and molecular "endotypes" may possibly be related with epithelial cell dysfunction and cellular senescence, changes in innate and acquired immunity, and abnormal lung remodeling.[7,9] The most important environmental factors include chronic microaspirations and changes in the lung microbiome,[9,10] while concomitant emphysema in smokers constitutes an important lifestyle factor.

The immediate question that has emerged is whether patients with different clinical or molecular phenotypes respond differently to antifibrotic treatments. Nintedanib and pirfenidone have pleiotropic effects and act effectively on different pathogenic pathways. In contrast, other more specific treatments (interferon-γ, ARES, anti-LOXL2 monoclonal antibody)[7] have been shown to be ineffective in non-selected IPF patients, despite preclinical evidence of their potential effectiveness. Studies are needed in order to establish whether all these possible phenotypes will be useful, and how the selection and stratification of patients in clinical trials can be improved.

In a chronic, progressive, and ultimately fatal disease such as IPF, an important therapeutic goal must be patient quality of life. Various "patient-reported outcomes" are being developed specifically for IPF.[11] Physical training programs, for instance, must form a part of the routine care pathway in patients with IPF, since these have shown benefits in exercise capacity, dyspnea, and quality of

☆ Please cite this article as: Bollo de Miguel E. Qué hay de nuevo en la fibrosis pulmonar idiopática. Arch Bronconeumol. 2018;54:1–2.

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life, although the design of these programs must be more precisely defined, and the duration of the effects is still unclear.

Multiple molecules[12] for the treatment of IPF, monoclonal antibodies in particular, are currently at the basic research or clinical trial stage. Some treatments are already available, and 2 phase IV studies (NCT02598193, NCT02579603) are currently evaluating the safety and tolerability of the combination of pirfenidone and nintedanib in IPF patients. This modality offers an alternative to sequential treatment in which the drug is switched if the first option becomes ineffective. Other treatments have also been proposed: 2 articles have been published on the possible benefit of statins[13] and the harmful effect of anticoagulants,[14] both indicated for reasons other than IPF in IPF patients. The debate on the usefulness of antacid treatment continues with the publication of a *post hoc* analysis of patients receiving placebo in 2 clinical trials,[15] in whom an increase in lung infections was observed, with no improvement in disease progression, mortality, or decline in FVC.

In conclusion, now that consolidated antifibrotic treatment is available for IPF, greater understanding of the complex mechanisms that underlie the appearance of pulmonary fibrosis has led to the design of better diagnostic strategies and paved the way for the development of new and more specific treatments.

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