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EDITORIAL

How to handle IPF – the new Portuguese consensus document

Idiopathic pulmonary fibrosis (IPF) is a serious, underdiagnosed, chronic progressive and ultimately fatal lung disease. Survival is worse than in many malignancies. The UIP pattern, either on HRCT or biopsy, is the morphologic hallmark but it is not specific for IPF. With two antifibrotic drugs now available for treatment it is crucial to make a precise diagnosis and differentiate IPF from other interstitial lung diseases with different prognosis and treatment approaches, especially from chronic hypersensitivity pneumonitis, idiopathic fibrotic NSIP and interstitial pneumonias with autoimmune features.

In the past decade, significant progress has been made in the field but many unresolved problems remain. We have learned that a secure diagnosis of a UIP pattern is possible by HRCT criteria alone without the need for histopathological confirmation.[1] It became evident that diagnostic security can be increased by multidisciplinary discussion and that bronchoscopic lung cryobiopsy is probably equally informative as surgical lung biopsy in this setting.[2] Many patients are not willing or are not advised to undergo surgical lung biopsy because it is a risky procedure particularly for those with severe disease and with marked comorbidities.

With the advent of pharmacological treatment options patients with IPF should be diagnosed quickly. This implies increased awareness of the disease by the general practitioner with the correct recognition of velcro-like crackles on auscultation in the elderly and consecutive prompt referal to an expert center for further studies. Unfortunately, the diagnosis of IPF is still frequently delayed, as evidenced in a recent interview of patient advocavy groups in 9 European countries regarding the care of IPF patients.[3] The feedback regarding the diagnosis of IPF showed that false diagnoses with other respiratory disorders are common, awareness of IPF guidelines is often poor and referral to specialists often significantly delayed.

Based on this background, the Portuguese consensus document for the diagnosis and treatment of IPF published in this issue of the Revista is a timely and well balanced expert statement.[4] Pneumologists, radiologists and pathologists elaborated a concise paper aimed to alert the health authorities about the relevance of early recognition of the disease and the challenges with the new drugs approved, and to give practical advice how to handle such a difficult disease. It is refreshing to see that the authors avoided producing another evidence-based guideline. The importance of a multidisciplinary approach, including the awareness of general practitioners, and experienced pulmonologists, radiologists and pathologists in the evaluation and correct treatment of diffuse interstitial lung disease, is clearly highlighted. The pitfalls with the identification of a definite UIP pattern on HRCT are addressed: the distinction between honeycombing and either traction bronchiectasis or paraseptal emphysema can be difficult even for an experienced radiologist, as demonstrated by the high interobserver variability in the assessment of honeycombing with only moderate kappa values of agreement ranging from 0.40 (non-chest expert radiologists) to 0.58 (expert chest radiologists).[5] Very wisely the Portuguese authors do not mention the frequent comorbidity of emphysema in IPF patients, thereby avoiding any discussion on combined pulmonary fibrosis and emphysema (CPFE),[6] and whether this is a distinct entity, or – what we rather believe – the coincidental existence of two diseases sharing the same risk factor cigarette smoking.

In regard to pharmacological treatment recommendations, the situation has completely changed since the publication of the ATS/ERS/JRS/ALAT 2011 guidelines on IPF[1] where a rather nihilistic view was expressed that no proven therapy exists for this disease, and 11 weak or strong negative recommendations were given. Within only four years, in the 2015 update of these guidelines,[7] conditional recommendations were made for the use of nintedanib and for pirfenidone. In this context, the authors of the Portuguese consensus document again took a wise approach by stating first that ''the therapeutic strategy in IPF should be individualized for each patient, considering the evaluation of potential benefits and risks'', and by stating next, just descriptively, that ''nintedanib and

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pirfenidone, two compounds with pleiotropic mechanisms of action are, to date, the two drugs with confirmed efficacy in slowing functional decline and disease progression in IPF patients'', thereby avoiding to grade the strength of the recommendation.

On the other hand, our Portuguese colleagues appear to be quite strict with their strong recommendation that ''according to the international recommendations,[1,7] asymptomatic GER should be treated in the majority of patients with IPF, namely with PPI''. This is based on a post-hoc analysis of data from three randomized controlled trials showing that IPF patients taking proton pump inhibitors (PPI) and/or H2 inhibitors had a significantly slower decline in FVC over time.[8] In contrast, however, a recent post-hoc analysis of the placebo arms of three pirfenidone trials (two CAPACITY and ASCEND) including 624 patients showed that anti-acid therapy (mainly PPIs) did not improve outcomes in patients with IPF and was even associated with an increased risk of infection in those with more advanced disease.[9] A post-hoc analysis of the INPULSIS trials with nintedanib showed similar findings with no differences in outcomes between patients with or without anti-acid therapy[10] Therefore, we would currently recommend PPI treatment only for those IPF patients with symptomatic GER, in agreement with the German IPF guideline,[11] and hope that this controversial issue will be clarified in the future with a prospective placebo-controlled PPI trial for IPF.

How to handle IPF? Many questions are still open and have not been addressed by our Portuguese colleagues. These include the question of how to treat a patient with probable or possible IPF compared to definite IPF, or with unclassifiable IIP. Should such a patient first be treated with antiinflammatory therapy? He might have the chance to respond if the diagnosis is not IPF but NSIP. If he would not respond, however, and progress like IPF, the diagnosis should be re-considered and changed into highly probable IPF. The consequence would be to switch therapy to an antifibrotic drug. This classification of IIPs or any ILD according to disease behaviour was newly introduced in the 2013 update of the international classification of the IIPs[12] and seems to be very relevant for patients without a clear diagnosis even after expert multidisciplinary discussion.

Many open questions are related to antifibrotic therapy, such as when to start and when to stop treatment, whether a stable asymptomatic patient with very mild disease should be treated, which drug to use first, when to switch therapy. What achievements will we see in the future? Will we ever get evidence from controlled trials that combination therapy is better than a single drug? Will gene polymorphisms or other biomarkers become available which accurately predict the response to a distinct antifibrotic drug? Much research is needed, but we are convinced that the landscape of IPF will change in the near future as rapidly as in the recent past, giving ample opportunities to re-write current guidelines and statements.

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