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The earlier, the better: Impact of early diagnosis on clinical outcome in idiopathic pulmonary fibrosis

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ABSTRACT

Background: Idiopathic pulmonary fibrosis (IPF) is a complex disease with a highly variable clinical course and generally poor prognosis. Classified as a rare disease, significant increases in incidence have been recorded worldwide in recent years. Left untreated IPF is extremely debilitating with substantial personal, social and economic implications.
Objectives: To discuss how IPF is diagnosed and managed in real life clinical practice with particular reference to Italy and to determine how new and effective therapies can be incorporated into a patient-centred management approach in order to improve the lives of patients with IPF.
Outcomes: Barriers to early diagnosis are discussed. Cited reasons for delays in diagnosing IPF in Italy include: inherent difficulties in diagnosis; lack of knowledge/awareness of the condition among point-of-contact healthcare professionals; delays in referral to centres of excellence and underestimation of symptoms by both patients and healthcare workers. Valid therapeutic options with demonstrated efficacy in slowing the decline in lung function are now available for patients with IPF. The ASCEND trial confirmed the effects of pirfenidone, approved for the treatment of IPF on the basis of the four phase III trials. Nintedanib, a tyrosine kinase inhibitor that targets the PDGF receptors α/β, FGF receptors 1 to 3, and VEGF receptors 1–3, is approved in the USA and the EU for the treatment of IPF. The TOMORROW and the INPULSIS placebo controlled trials in patients with IPF confirm the efficacy and safety of nintedanib and recent interim analyses endorse its long-term effects in slowing disease progression.
Conclusions: The importance of early and accurate diagnosis of IPF cannot be underestimated and it is the duty of all healthcare professionals to be vigilant to the symptoms of IPF and to involve a multidisciplinary team in diagnosing and managing IPF early in the course of disease.

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Contents

1. Introduction

Idiopathic pulmonary fibrosis (IPF), a chronic progressive interstitial lung disease (ILD), is characterized by breathlessness (initially only on exertion) and dry cough that interfere with daily activities. Other features include bibasilar inspiratory crackles, deteriorating pulmonary function tests and finger clubbing [1–3]. It is an extremely complex disease with a highly variable clinical course. Progression may take a number of forms — slow worsening of the severity of dyspnoea, rapid deterioration and progression to death or relative stability interposed with periods of acute respiratory decline sometimes manifest by hospitalizations for respiratory failure [4,5]. Over time there is an irreversible loss of lung function with median survival around three years from diagnosis [6].

Although the exact mechanisms underlying the development of IPF remain elusive, it is thought that repetitive lung injury, such as that associated with cigarette smoke, industrial dusts, gastro oesophageal reflux and viral infection, leads to alveolar epithelial cell injury and activation [2,3,7,8]. This results in the recruitment, proliferation and activation of mesenchymal cells and the formation of fibroblastic foci and abnormal accumulation of extracellular matrix (ECM) that mirror abnormal wound repair. Abnormal extracellular matrix deposition and excessive collagen accumulation cause progressive fibrosis and stiffening of the lungs. Beyond these cellular and tissue changes there is evidence that growth factors including platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) play a role in the development and progression of IPF [9,10]. Not all individuals exposed to these stimuli go on to develop IPF, suggesting that affected individuals may be predisposed to the condition, possibly influenced by genetic abnormalities and aging.

The publication of international, evidence-based guidelines for the diagnosis and management of IPF represented a major step forward as did the introduction of new treatments with demonstrated efficacy and tolerability that modify symptoms and alter disease course. The goals of this review are multifold: to review up-to-date information on the incidence/prevalence of IPF with particular reference to Italy; to discuss how IPF is diagnosed and managed in real life clinical practice and to determine how new and effective therapies can be incorporated into a patient-centred management approach in order to improve the lives of our patients.

1.1. Idiopathic pulmonary fibrosis: burden of illness

Although IPF is classified as a rare disease, it accounts for 17–37% of all interstitial lung disease (ILD) and its social, healthcare and economic implications are significant [6,11]. Data on the prevalence and incidence of IPF remain unclear, mainly because of the lack of a consistent definition as well as the different diagnostic methods used. A US study reported the prevalence of IPF was 2.7 cases per 100,000 in those aged 35–44 years old and 175/100,000 in those over the age of 75 years [3,12]. On the other hand, a recent study on US Medicare beneficiaries from 2001 to 2011 showed higher rates with a prevalence of 494.5/100 000 in 2011. Prevalence increased annually, even in the subgroups based on more restrictive algorithms for diagnosis [13]. In the United Kingdom the incidence of and registered deaths from IPF continues to rise — at present there are about 15,000 patients with a diagnosis of IPF and because of its poor prognosis 5000 deaths per year [11,14].

Historically, the epidemiology of IPF in Italy has been a neglected area of research but two recent studies — one conducted in the Central-South and one in the North —provided much needed up-to-date information [15,16]. In the Lazio study (6 million inhabitants) the annual prevalence and incidence of IPF were estimated at 25.6/100,000 and 7.5/100,000 using the ICD9-CM code 516.3 without chart audit and 31.6/100,000 and 9.3/100,000 for the IPF 'confident' definition after hospital chart [15]. In the study conducted in Lombardy (10 million inhabitants) depending on the algorithms used (generic, broad and narrow case definition) prevalence rates of 35.5, 22.4, and 12.6/100,000 person-years were recorded with an observed increase in prevalence over the years [16]. These data confirm that in Italy as in other countries, the incidence of IPF is increasing with rates and regrettably prognosis, similar to those of some forms of cancer.

The growing incidence, the variability and irreversibility of its clinical course, as well its inevitable progression mean that anti-fibrotic therapy should be discussed with patients in a timely manner after first diagnosis. However, obtaining an early and accurate diagnosis of IPF is not straightforward and necessitates the