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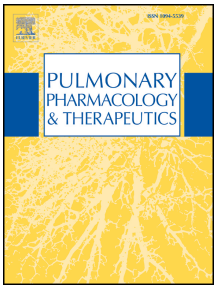

The earlier, the better: Impact of early diagnosis on clinical outcome in idiopathic pulmonary fibrosis

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PII: S1094-5539(16)30132-8

DOI: 10.1016/j.pupt.2017.02.005

Reference: YPUPT 1592

To appear in: *Pulmonary Pharmacology & Therapeutics*

Received Date: 17 October 2016

Revised Date: 3 February 2017

Accepted Date: 27 February 2017

Please cite this article as: Aiello M, Bertorelli G, Bocchino M, Chetta A, Fiore-Donati A, Fois A, Marinari S, Oggionni T, Polla B, Rosi E, Stanziola A, Varone F, Sanduzzi A, The earlier, the better: Impact of early diagnosis on clinical outcome in idiopathic pulmonary fibrosis, *Pulmonary Pharmacology & Therapeutics* (2017), doi: 10.1016/j.pupt.2017.02.005.

Review article

Title: 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.

Key words: Idiopathic pulmonary fibrosis, pirfenidone, nintedanib, TOMORROW, INPULSIS, diagnosis

1.1 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 [**1,2,3**]. 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.

2.1 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 [**11,6**]. 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 [**12,3**]. On the other hand, a recent study on US Medicare beneficiaries from 2001–2011 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 antifibrotic 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 collaborative expertise of a multidisciplinary team (MDT) including respiratory physicians, radiologists and histopathologists.

3.1 Ensuring an early and accurate diagnosis of idiopathic pulmonary fibrosis

3.1.1 Clinical features

IPF should be considered in all adult patients with unexplained chronic exertional dyspnoea. It commonly presents with cough, bibasilar inspiratory crackles also known as Velcro® crackles (because the sound is similar to that produced when Velcro® is detached), and finger clubbing [**17**]. Physical examination of the chest reveals crackles not editable with coughing throughout the inspiratory phase. These breath sounds are present from the early stages of the disease and although Velcro® crackles are not peculiar to IPF, their presence in subjects aged ≥ 60 years, should rise the suspicion of IPF [**17,18,19,20**].

3.1.2 Radiological and histopathological features

The gold standard imaging test for suspected IPF is high-resolution computed tomography (HRCT), which should be carried out as early as possible after symptoms first appear. The new international diagnostic criteria for radiology and histopathology are more precise than previous versions and include three HRCT categories: usual interstitial pneumonia (UIP), possible UIP and inconsistent with UIP patterns and four histological categories: UIP, probable UIP, possible UIP and not UIP [**2,17**] (**Tables 1 and 2**).

Table 1. High-resolution computed tomography criteria for usual interstitial pneumonia (UIP) pattern in idiopathic pulmonary fibrosis (IPF)

UIP Pattern - All Four Features
1 Subpleural, basal predominance
2 Reticular abnormality
3 Honeycombing with or without traction bronchiectasis
4 Absence of features listed as inconsistent with UIP pattern
Possible UIP Pattern - All Three Features
1 Subpleural, basal predominance
2 Reticular abnormality

3 Absence of features listed as inconsistent with UIP pattern
Inconsistent with UIP Pattern - Any of the Seven Features
1 Upper or mid-lung predominance
2 Peribronchovascular predominance
3 Extensive ground glass abnormality (extent > reticular abnormality)
4 Profuse micronodules (bilateral, predominantly upper lobes)
5 Discrete cysts (multiple, bilateral, away from areas of honeycombing)
6 Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes)
7 Consolidation in bronchopulmonary segment(s)/lobe(s)

Table 2. Histological criteria for usual interstitial pneumonia (UIP) pattern in idiopathic pulmonary fibrosis (IPF)

UIP Pattern (All Four Criteria)	Probable UIP Pattern	Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Criteria)
d Evidence of marked fibrosis/architectural distortion, ± honeycombing in a predominantly subpleural/paraseptal distribution d Presence of patchy involvement of lung parenchyma by fibrosis d Presence of fibroblast foci d Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)	d Evidence of marked fibrosis / architectural distortion, ± honeycombing d Absence of either patchy involvement or fibroblastic foci, but not both d Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column) OR d Honeycomb changes only‡	d Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation d Absence of other criteria for UIP (see UIP PATTERN column) d Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)	d Hyaline membranes* d Organizing pneumonia*† d Granulomas† d Marked interstitial inflammatory cell infiltrate away from honeycombing d Predominant airway centered changes d Other features suggestive of an alternate diagnosis

Definition of abbreviations: HRCT 5 high-resolution computed tomography; UIP 5 usual interstitial pneumonia.
* Can be associated with acute exacerbation of idiopathic pumonary fibrosis.
† An isolated or occasional granuloma and/or a mild component of organizing pneumonia pattern may rarely be coexisting in lung biopsies with an otherwise UIP pattern.
‡ This scenario usually represents end-stage fibrotic lung disease where honeycombed segments have been sampled but where a UIP pattern might be present in other areas. Such areas are usually represented by overt honeycombing on HRCT and can be avoided by pre-operative targeting of biopsy sites away from these areas using HRCT.

The presence of honeycombing with or without traction bronchiectasis can make the diagnosis of UIP pattern difficult using HRCT alone; further workup is required if a HRCT scan shows features of possible and/or inconsistent UIP patterns [**17**]. The presence of a radiological and/or histological UIP pattern is not per se sufficient to establish the diagnosis of IPF and a definite diagnosis requires the exclusion of other known causes of ILD, as well as the presence of a definite UIP pattern on chest HRCT and specific combinations of chest HRCT/histopathology patterns. There is evidence that patients with IPF can be accurately diagnosed without a surgical lung biopsy (SLB). In fact, in around two thirds of cases an SLB is not required and a definitive diagnosis of IPF is possible based on HRCT thorax alone [**21**] (**Table 3**, **Figure 1**).

Table 3. Combination of high-resolution computed tomography (HRCT) and surgical lung biopsy for the diagnosis of idiopathic pulmonary fibrosis (IPF)

HRCT Pattern	Surgical Lung Biopsy Pattern (When Performed)	Diagnosis of IPF?
UIP	UIP or Probable UIP or Possible UIP or Non-classifiable fibrosis	YES
	Not UIP	No
Possible UIP	UIP or Probable UIP	YES

	Possible UIP or Non-classifiable fibrosis	Probable
Inconsistent with UIP	Not UIP	No
	UIP	Possible
	Probable UIP or Possible UIP or Non-classifiable fibrosis or Not UIP	No

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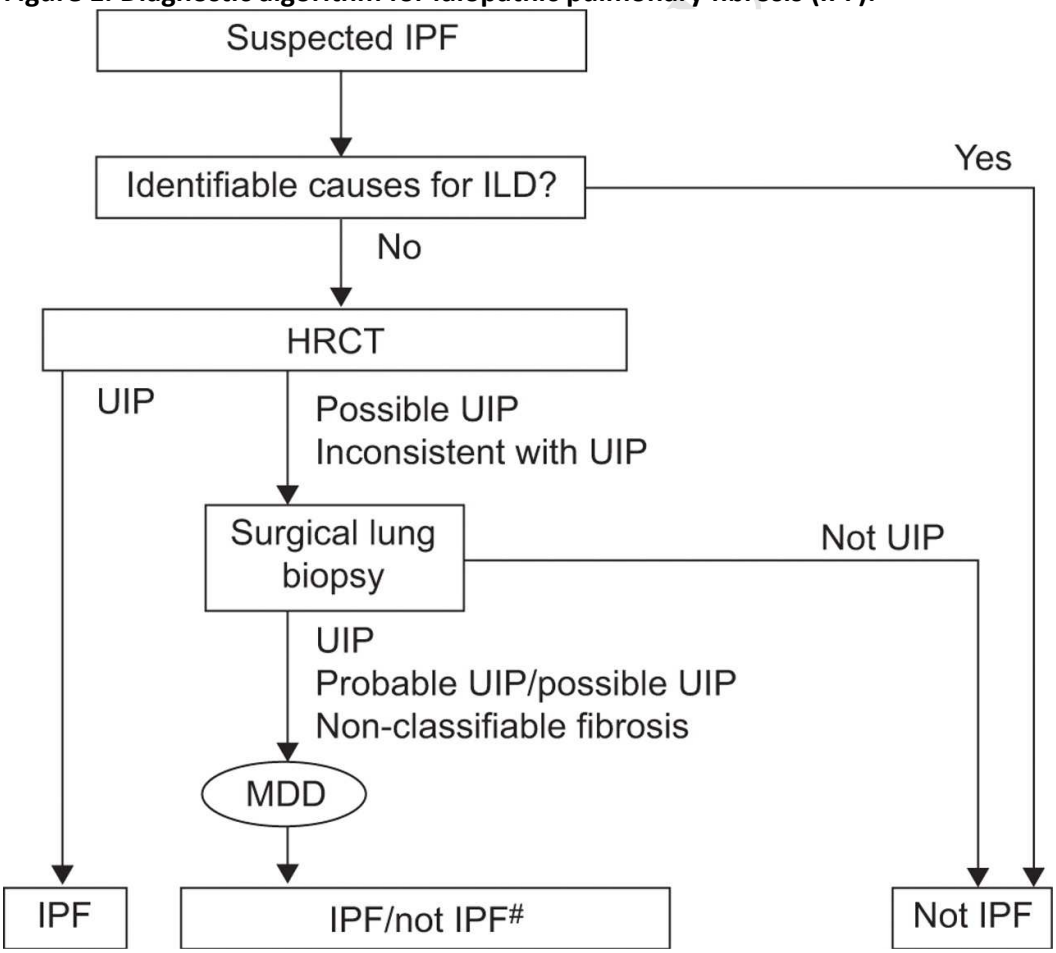
G. Raghu et al. 2011 An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 183, 6 788–824.
The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

Figure 1. Diagnostic algorithm for idiopathic pulmonary fibrosis (IPF).



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Patients with suspected IPF (i.e. patients with unexplained dyspnoea on exertion and/or cough with evidence of interstitial lung disease [ILD]) should be carefully evaluated for identifiable causes of ILD. In the absence of an identifiable cause for ILD, an HRCT demonstrating UIP pattern is diagnostic of IPF. In the absence of UIP pattern on HRCT, IPF can be diagnosed by the combination of specific HRCT and histopathological patterns. Therefore, international guidelines advocate for interdisciplinary discussion of these cases.

In patients without a biopsy the diagnosis may be established if ILD is present and HRCT shows a UIP pattern. When a biopsy is required, diagnosis is made based on specific combinations of HRCT and SLB aspects showing a UIP pattern [**12**,**11**]. Overall the use of SLB is in decline, as it is no longer considered to be essential in making a diagnosis given the high-quality evidence regarding HRCT specificity for the recognition of UIP pattern. The introduction of less-invasive methods, such as the transbronchial lung cryobiopsy (TBLCB), have the potential to transform the diagnosis of IPF in clinical practice as they can be used to obtain samples large enough to morphologically support the multidisciplinary diagnosis of interstitial lung disease [**22,23**]. In a recent literature review Ravaglia et al. concluded that in the diagnosis of interstitial lung diseases (ILDs) surgical lung biopsy (SLB), is associated with significant morbidity and mortality and also appreciable costs and that cryobiopsy is safe and has lower complication and mortality rates compared to SLB. TBLC might therefore, be considered the first diagnostic approach for obtaining tissue in ILDs, reserving the

surgical approach for cases in which TBLC is not diagnostic [**24**]. However, although the technique appears to be safer than surgical lung biopsy, it is not without complications. Casoni et al advised its safety needs to be investigated in large multicentric trials before it is widely adopted [**25**]. Bleeding and pneumothorax (reported in about 5% of cases) are the most often reported adverse events and the routine preventive use of a Fogarty catheter does not allow the real incidence of bleeding complications to be evaluated. Johannson et al. reasoned that the diagnostic accuracy of TBLCB cannot be determined given the absence of comparative studies, and while the histopathological and multidisciplinary discussion-based diagnostic yield of TBLCB appears high, the implications of pneumothorax and moderate-to-severe hemorrhage should not be underestimated [**26**].

3.1.3 Other investigations

Bronchoalveolar lavage (BAL) is used to exclude conditions such chronic hypersensitivity pneumonitis (HP), sarcoidosis or connective diseases but its role in the diagnosis of IPF is much debated [**27,28,29,30**].

Transbronchial lung biopsy (TBB) is useful in excluding other interstitial lung diseases such as sarcoidosis or malignancies and infections but neither current nor previous recommendations propose TBB in the diagnosis of IPF [**31**]. It may be that in the right clinical setting and with appropriate tissue sampling TBB can support a diagnosis of UIP. In fact it has been shown that using a novel technique for TBB – transbronchial cryobiopsy, the size of TBB samples were much larger than those obtained using forceps.

Serological testing for connective tissues diseases is considered to be part of routine diagnostic workup of IPF in most patients whether there is a manifestation of connective tissue disease (CTD) or not although a study by Lee et al. showed that circulating autoantibody positivity is no more common in patients with IPF than in healthy, age-similar adults, and that patients with IPF and circulating autoantibodies do not represent a distinct clinical phenotype. [**1,2,17,32,33,34**]. Nevertheless, published guidelines suggest serologic evaluation should be performed even in the absence of signs or symptoms of connective tissue disorder and should include rheumatoid factor, anti-cyclic citrullinated peptide (anti-CCP) and anti-nuclear antibody titre (ANA) but other serological tests such as anti-synthetase antibodies, creatinephosphokinase and aldolase, Sjogren's antibodies and scleroderma antibodies may be indicated in appropriate clinical cases [**32**]. Signs of connective tissue disorders such as arthritis, Raynaud's phenomenon, skin changes, abnormal oesophageal motility should be investigated before IPF is confirmed [2]. Finally, a number of biomarkers are under investigation but this field is still very much in the early stages and as yet not generally accessible for routine clinical use [**35,36**].

3.1.4 Genotypes phenotypes and comorbidities

Different phenotypes of IPF may have different rates of progression and the existence of comorbidities can influence prognosis [**37**]. Although it was thought that IPF was a slowly progressive disease it may be that there is an accelerated variant phenotype. Combined pulmonary fibrosis and emphysema, and disproportionate pulmonary

hypertension in IPF may also be distinct phenotypes. Further investigation is required to characterise these phenotypes and to establish if there is a biological explanation for these phenotypes [**22**].

Familial IPF – defined as two or more verified cases within a group of relatives belonging to a primary family unit – accounts for 0.5-2.0% of all cases of IPF [**3,36,38**]. Clinical features of familial IPF are the same as the sporadic form and they are histologically indistinguishable except the former usually has an earlier age at onset.

Effective management of IPF also involves identifying and treating comorbidities to improve overall quality of life (QoL) and wellbeing of patients. IPF is associated with both respiratory and non-respiratory comorbidities. The most frequent is cardiovascular disease (CVD) that is more common as the disease progresses. Other comorbidities include pulmonary hypertension, emphysema, chronic obstructive pulmonary disease (COPD), sleep-related respiratory disorders, gastro-oesophageal reflux and lung cancer. It has been reported that the risk of developing lung cancer is approximately seven-times higher in patients with IPF compared to a control population even after adjustment for age, sex, and smoking history [**39**]. Although the reasons for this increase are not clear it has been suggested that the IPF lung is specifically predisposed to developing malignancy. Lung cancer has a significant impact on survival of patients with IPF — reducing survival by approximately 2 years [**22**]. Most patients with IPF have associated comorbid conditions, which negatively affect functional status, quality of life, and survival. Comorbid conditions can be pulmonary or extrapulmonary. Pulmonary comorbidities include pulmonary hypertension,

emphysema, and lung cancer, while non-pulmonary conditions include venous thromboembolism, coronary artery disease, congestive heart failure, sleep-disordered breathing, gastro-oesophageal reflux disease, and anxiety or depression [**40**]. The identification and prompt treatment of comorbidities can have a significant impact on overall outcome **[41**]. IPF alone and in combination with comorbidities significantly impairs QoL and imposes a substantial burden on health care resources [**42**].

4.1 Addressing unmet needs in idiopathic pulmonary fibrosis: importance of early diagnosis

The diagnosis of IPF is often made late in the disease course for a number of reasons — patients may present to their physicians having had 'non-specific' symptoms, such as non-productive cough, exertional dyspnoea for months/years previously or they may have been diagnosed with other more common respiratory diseases such as asthma or COPD before IPF is finally diagnosed [**43**]. Kim et al. reported that 1–3 years may elapse between the onset of symptoms and the specialist's assessment, while the delay in diagnosis can even increase up to 5 years [**44]**. A survey of IPF patients from five different European countries showed that in 58% of patients the time between disease onset and diagnosis was 1 year and 55% of patients interviewed had consulted at least three physicians before receiving the correct diagnosis [**45**].

There is a dearth of information on how IPF is diagnosed and managed in Italy and how it compares with other countries. To this end we conducted an *ad hoc* survey among our group of respiratory medicine specialists working in 8 IPF authorized prescriber

centres in Italy. Overall there was a total of 379 patients with IPF, 101 (26.7%) of which were new cases diagnosed in the preceding year (**box**). Of these, 55% presented for the first time with moderate stage IPF, 30% when IPF was already severe and only 15% first presented with early stage. Importantly results of the survey elucidated the main reasons why diagnosis of IPF in Italy is delayed: 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 symptoms underestimated by both patients and healthcare workers.

Overview of patients treated in eight IPF authorized prescriber centres in Italy

- Total of 379 patients in 8 centres (Alessandria, Chieti, L'Aquila, Naples, Pavia, Parma, Rome, Sassari).
- Of these 101 (26.6%) diagnosed in the previous year.
- Mean overall percentage of patients who presented with early, moderate IPF or severe IPF were 15%, 55% and 30%, respectively.
- The majority of patients presented with a honeycomb pattern on imaging.
- Reasons for patients presenting at specialist centres – first visit due to symptoms, referred by pneumonologist, family doctor, cardiologist, radiologist, rheumatologist.

Nearly half of IPF patients show a decline in FVC and the greater is the FVC decline the higher is the increased risk of IPF progression and mortality. It therefore follows that prompt interventions to slow FVC decline may help improve clinical outcomes in patients with IPF [**46**]. Until the introduction of new therapies delays in diagnosis did not have a significant impact on disease progression/survival. However, now that effective therapies are available, early diagnosis is paramount to optimize clinical management. In addition, in this era of cost containment within health care systems

earlier diagnosis may in fact be more cost-effective as delayed diagnosis of IPF is associated with increased costs in terms of investigations performed [**4,47**].

5.1 Pharmacological strategies for the management of idiopathic pulmonary fibrosis: shifting the paradigm

The objectives of treatment in IPF are to reduce symptoms, slow/stop progression, prevent acute exacerbations and ultimately to prolong survival. In the past couple of decades major advances in our understanding of the pathogenesis of IPF have been made and these developments are paralleled with the introduction of pharmacological treatments to effectively manage the condition. Disappointing results were obtained previously with therapeutic agents targeting inflammatory pathways as IPF was considered to be a chronic inflammatory response resulting in progressive pulmonary fibrosis. More recently, agents targeting the biological process that drive fibrosis have been shown to be effective in IPF. We have seen that VEGF, FGF and PDGF, mediate fibrogenesis and angiogenesis, and are hence implicated in the pathogenesis of IPF.

Pirfenidone an oral antifibrotic agent was approved for the treatment of IPF in Japan, Europe, India, and Canada on the basis of the international phase III trials but due to the conflicting results of the Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes (CAPACITY) trials, the US FDA requested a further confirmatory trial [**48**]. Results of the Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND) trial in 555 patients with IPF, randomized to receive either pirfenidone or placebo provided confirmation of its effects [**49,50,51**]. A retrospective real-life study in major ILD centres in Italy, evaluated the effect of pirfenidone on disease progression in 128

patients with IPF (48 mild, 64 moderate IPF and 8 severe). Decline in lung function, monitored during one-year treatment with pirfenidone was compared with the decline measured during the one-year pre-treatment period [**51**]. At baseline (first pirfenidone prescription), mean percentage forced vital capacity (FVC) was 75% (35-143%) of predicted, and mean percentage diffuse lung capacity (DLCO) was 47% (17-120%) of predicted. Overall, pirfenidone attenuated the decline in FVC (p=0.065), but did not influence the decline in DLCO (p=0.355) in comparison to the pre-treatment period. Stratification of patients according to %FVC level at baseline (>75% and ≤75%) and GAP index at baseline (stage I vs. II/III) showed that attenuation of decline in lung function was more pronounced in patients with more severe disease. The authors suggest that since pirfenidone was beneficial in patients with moderate-severe disease, it might also be effective in patients with more advanced disease [**52**].

Because IPF is a highly heterogeneous disease with variable disease course, obtaining accurate data from individual clinical trials enrolling limited numbers of patients is challenging. Pooling and analysing data from trials with similar design, patient populations and outcomes, enables clinicians to obtain greater insight into the effects of a given therapy. Noble et al. and Nathan et al. published the results of pooled analyses of the two CAPACITY trials and the ASCEND trial [**53,54**]. The Noble analysis included 1247 patients randomised to pirfenidone 2403/mg/day or placebo in the CAPACITY or ASCEND studies. At 1 year, pirfenidone reduced the proportion of patients with a ≥10% decline FVC % Pred or death by 43.8% (95% CI 29.3–55.4%) and increased the proportion of patients with no decline by 59.3% (95% CI 29.0–96.8%). A treatment benefit was also observed for progression-free survival, 6-min walk distance and

dyspnoea. Gastrointestinal and skin-related adverse events were more common in the pirfenidone group, but rarely led to discontinuation. The authors concluded that results provide the most stable and robust estimates to date of the magnitude of the treatment effect of pirfenidone on multiple measures of IPF disease progression and provide further evidence to support the clinically meaningful treatment benefit and acceptable safety profile of pirfenidone in patients with IPF. Similarly Nathan et al concluded that pirfenidone is associated with a reduction in the relative risk of mortality compared with placebo over 120 weeks [**54**]. Albera et al. in a post-hoc analysis of the same patient group showed efficacy of pirfenidone in patients both with more preserved lung function (FVC ≥80% or GAP stage I) and well as in those with less preserved lung function (FVC <80% or GAP stage II-III), supporting the initiation of treatment with pirfenidone, irrespective of stage of baseline lung function [**55**].

Nintedanib (Ofev®; Boehringer Ingelheim, Germany), 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 [**1,56,57**]. Nintedanib is available in Italy with the name Ofev® [**58**]. The efficacy and safety of nintedanib has been confirmed in three landmark international phase II/III placebo controlled trials in patients with IPF and more recently in subgroup analyses and pooled/meta-analyses [**59-62**]. In the TOMORROW phase II, placebo-controlled, 52-week, dose-finding trial, 428 patients with IPF were randomized to one of four doses of nintedanib (50mg daily, 50mg bid, 100mg bid, or 150mg bid) using a stepwise increasing dose approach [**59**]. Nintedanib (150mg bid) reduced the annual rate of decline of FVC and lowered the incidence of acute exacerbations compared with placebo with an acceptable safety and

tolerability profile **[59].**

Following the encouraging results of the TOMORROW trial, two replicate randomised, placebo-controlled, 52-week phase III studies – the INPULSIS® trials – were conducted [**61**]. Patients were randomized to receive nintedanib 150mg bid (309 patients in INPULSIS-1 and 329 in INPULSIS-2) or placebo (204 patients in INPULSIS-1 and 219 in INPULSIS-2). In both trials nintedanib significantly reduced the annual rate of decline in FVC compared with placebo. In INPULSIS®-2, there was a significant difference in favour of nintedanib on time to first acute exacerbation and change from baseline in SGRQ (St. George's Respiratory Questionnaire total score, a measure of QoL). The tolerability of nintedanib was manageable for most patients, Among the patients in the nintedanib groups who had diarrhoea, most reported events that were of mild or moderate intensity (93.7% in INPULSIS-1 and 95.2% in INPULSIS-2).

The similar design of the TOMORROW and INPULSIS trials and the consistent results observed on the primary endpoint meant that data from these three trials (1231 patients: 723 nintedanib, 508 placebo), could be combined (pooled and meta-analyses) to determine the overall efficacy and safety of nintedanib (150mg bid) [**61,63**]. In general, treatment effect sizes were similar across the pooled and meta-analyses. Nintedanib consistently slowed disease progression by significantly reducing the annual rate of decline in FVC compared with placebo [**64**]. In the pooled analysis, the hazard ratio (HR) for time to first acute exacerbation was 0.53 ([95% CI: 0.34, 0.83]; p=0.0047), in favour of nintedanib. The proportion of patients with 1 acute exacerbation was 4.6% in the nintedanib group and 8.7% in the placebo group [**62**]. Importantly, an analysis of

deaths occurring between randomization and the end of the follow-up period (28 days after last study drug intake in the INPULSIS trials and a maximum of 14 days after last study drug intake in the TOMORROW trial), showed a significant 43% reduction in risk in favour of nintedanib (HR: 0.57;95% CI: 0.34–0.97; p = 0.0274) [**57**]. A 30% reduction in the risk of all-cause mortality was observed with nintedanib versus placebo over 52 weeks (HR 0.70 [95% CI: 0.46, 1.08]; p=0.0954). Overall the percentage of patients who died from a respiratory cause was 3.6% and 5.7% in the nintedanib and placebo groups, respectively [**62**].

Post-hoc subgroup analyses from the pooled INPULSIS® clinical trials demonstrated a consistent effect of nintedanib in patients with different degrees of lung function impairment and different radiologic patterns in imaging tests at baseline (no honeycombing and no confirmation of diagnosis in lung biopsy vs. patients with honeycombing and/or biopsy confirmation of diagnosis) [**56,65**]. The most frequently reported adverse event in the INPULSIS® trials was diarrhoea (reported in 62% of patients compared with 18% with placebo) that led to premature treatment discontinuation in fewer than 5% of nintedanib-treated patients [**61**]. More than 90% of eligible patients (734/807) chose to receive open-label nintedanib in the on-going INPULSIS®-ON extension trial. A recent interim analysis confirmed the long-term efficacy and safety of nintedanib, with the beneficial effect of nintedanib on slowing disease progression maintained in the long-term and the change from baseline in FVC consistent over 2 years. The INPULSIS® trials enrolled a wide range of patients including those with mild FVC impairment at baseline (FVC >90% predicted) and the proven clini-

cal efficacy of nintedanib in slowing disease progression emphasizes the important of early preventive care with an effective symptom-based treatment.

6.1 A multidisciplinary team approach to optimise diagnosis and management of patients with idiopathic pulmonary fibrosis

It is universally accepted that the accuracy of the diagnosis of IPF increases when a MDT is involved. Accordingly, the international guidelines on the diagnosis and management of IPF state 'careful exclusion of alternative aetiologies through a multidisciplinary discussion (MDD) between pulmonologists, radiologists, and pathologists experienced in the diagnosis of ILD is of the utmost importance to an accurate diagnosis' in particular in those cases where the radiological patterns do not agree **[2**]. A diagnosis made by a MDT after exchange of clinical, radiographic information, often differs from the initial diagnosis made by an individual team member working alone and that interaction between clinicians, radiologists, and pathologists improves diagnostic confidence [**66,67**]. Delayed access to a specialist centre was associated with higher mortality in IPF, independently of disease severity [**47**]. Ultimately, correct and early diagnosis of IPF cannot ignore the collaboration of general practitioners as the first port of call for patients with nonspecific symptoms.

In our survey most patients (41%) were referred to our specialist centres by other respiratory pulmonologists; 18.0% presented at our centres as a first visit due symptoms; 7% were referred by a general practitioner; 13% by a radiologist and 6% by a cardiologist. All of the ten Italian centres surveyed had the possibility of consultation with a MDT composed (variably) of pulmonologists, radiologists, thoracic surgeons,

cardiologists, immunologists, rheumatologists and pathologists on an impromptu basis and in only 3/10 centres there was a formalised MDT. Encouragingly our survey showed the majority of centres (6/10) actively collaborate with other centres of excellence in Italy but in only 4/10 centres there was an active patient organisation.

Input from the MDT is vital in obtaining an early and accurate diagnosis, which is in turn essential to initiate therapies that have the potential to reduce disease progression. It should be remembered however that the role of the MDT does not stop with the diagnosis but is important at all stages of the disease from diagnosis through to treatment and eventually the palliative phase. Clinical signs and symptoms change over time and it is only by constant vigilance and re-evaluation that the efficacy of management strategies is ensured. Also the composition of the MDT should not be fixed over time, as the specialist skills necessary at the diagnostic phase are different from those at the palliative phase. To take one example — patients and patient groups often iterate that travelling long distances to specialist centres becomes increasingly difficult for patients with deteriorating respiratory function, so wherever possible, shared care between local and specialist centres should be provided and the MDT should include healthcare professionals experienced in palliative care. Likewise, in view of the impact of IPF diagnosis and prognosis it is important not to underestimate that patients and caregivers may require psychological support. Most centres in Italy already use the MDT approach but often this is on an *ad hoc* basis and is not a formalised part of patient care as resources are limited.

6.1.1 Lung transplantation — a neglected area

In patients with IPF, lung transplantation reduces the risk of death by 75% compared with patients who remain on the waiting list and transplantation is a recognized therapeutic option for patients with IPF, representing 35% of transplant recipients. Current outcomes in lung transplantation for IPF show significant survival benefits with 1-, 5-, and 10-year survival rates 74%, 45%, and 22%, respectively [**68**]. Although, these survival rates are significantly poorer than those for other causes of end stage lung disease, the possibility of lung transplantation should be taken into account when forming the MDT. It is also vital that an effective regional and national network is in place to make sure that patients with IPF are given the possibility of a lung transplant.

As new therapies for IPF emerge a more patient-centred approach becomes more than a priority. Patient groups and not-for-profit organizations play a key role in providing information and resources but also in raising awareness of the disease at an administrative level. Feedback we receive from patients and their families indicate that there is an urgent need for more healthcare support and education including prompt referral to specialist centres and timely diagnosis.

7.1 Conclusion

After many years in the wilderness IPF is getting the attention it deserves – valid therapeutic options with demonstrated efficacy in slowing the decline in lung function are available for patients with IPF. The importance of an 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 MDT in diagnosing and managing IPF early in the course of disease.

Our experience in Italy confirms published data showing that there are still large unmet medical, social and economic needs [**69**]. Left untreated IPF is an extremely debilitating disease and one that patients struggle to understand fully. The first challenge to address is increasing patient and physician knowledge of IPF. From the outset, patients, their families and their advocates need to be given clear and consistent information on the course, management, and care of their condition. Academic and practicing physicians need to work together to better define and disseminate information about IPF and to motivate providers to provide the necessary resources to ensure timely diagnosis and effective management of IPF.

Conflict of Interest Statements, Funding Source Declarations, Author Agreements/ Declarations and Permission

Acknowledgements: The authors thank EDRA for editorial support. This support was sponsored by Boehringer Ingelheim Italia Spa

Conflict of Interest:

- Prof. A . Sanduzzi received fees and contribution to research by Roche and Boehringer ingelheim.
- Dr. E. Rosi received fees from Boehringer Ingelheim and Roche.
- Dr. M. Bocchino received fees from Boehringer Ingelheim, Intermune and Roche.

Funding Source Declaration:

Authors did not receive funding for the realization of this manuscript.

Author Declaration: All authors have seen and approved the final version of the manuscript. The article is the authors' original work, has not received prior publication and is not under consideration for publication elsewhere.

Permission Note: Permission has been received to reproduce any material in the manuscript that is not original content.

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