Challenges in IPF diagnosis, current management and future perspectives

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Abstract. Recent developments have clarified our understanding of IPF and improved outcomes with two viable new therapeutic options, pirfenidone and nintedanib. In spite of these advances, questions and challenges concerning IPF still remain. Here we will focus on some of these unresolved areas: the diagnosis of IPF is hindered by limitations in current practice guidelines, surgical lung biopsy is contraindicated in many patients, the accuracy of prognostic evaluation needs to be increased and tolerability factors can jeopardise adherence to treatment. We will also identify new developments shaping the future of IPF management such as cryobiopsy, increased understanding of genetic factors and new treatment paradigms, which may help to fulfil currently unmet needs. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32; Suppl 1: 28–35)*

Key words: idiopathic pulmonary fibrosis; guidelines; staging; cryobiopsy; pirfenidone; genetics

Introduction

Idiopathic pulmonary fibrosis (IPF) is characterised by progressive dyspnoea and typically culminates in respiratory failure within 5 years of diagnosis (1,2). As IPF is the most prevalent idiopathic fibrotic lung disease, is more prevalent than many cancers and has a worse outcome than most cancers, it has been the focus of considerable research activity over the past years, and these efforts have generated significant advances. In fact, the period between 2011 and 2014 has seen pivotal developments that have increased our understanding of IPF and improved short-term outcomes with two viable new therapeutic options, pirfenidone and nintedanib (3-6).

In spite of these advances, questions and challenges concerning IPF still remain. Here we will focus on unresolved difficulties currently associated with diagnosis and treatment as well as identify emerging directions shaping the future of IPF management.

Diagnostic challenges

Limitations of practice guidelines

In 2011, the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society and the Latin American Thoracic Association issued evidence-based, joint guidelines on the diagnosis and management of IPF (1). While these guidelines undoubtedly constitute an advance from the previous guidelines published in 2000 (ATS/ERS), their value today is limited. First, the

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treatment landscape has been considerably altered since 2011, with data and clinical experience with the antifibrotic drugs pirfenidone and nintedanib changing the way we look at IPF. Secondly, the guidelines fail to provide clear direction on how to manage patients with probable/possible IPF (1,7).

According to the diagnostic algorithm in the 2011 guidelines, all patients with suspected IPF should undergo high-resolution computed tomography (HRCT). If a usual interstitial pneumonia (UIP) pattern is present, the patient is considered to have IPF and if a UIP pattern is absent the patient does not have IPF. If HRCT findings show possible UIP, or are inconsistent with UIP, it is recommended that patients undergo surgical lung biopsy (SLB), followed by multidisciplinary team diagnosis. At least 45% of patients have an inconclusive HRCT, but many are not good candidates for SLB due to factors such as severe disease, old age, comorbidities, lack of timely access and patient preference (8). The current guidelines make no recommendation about how to manage these patients.

Reaching a definitive diagnosis is critical to directing treatment decisions. Results of the PANTHER-IPF trial, which showed that triple therapy with prednisone, azathioprine, and N-acetylcysteine increased the risk of death and hospitalisation in patients with IPF, underscore the necessity of distinguishing between IPF and other forms of ILD (9).

In real-world practice, a working diagnosis of IPF or non-IPF can be made in the absence of biopsy, based on multidisciplinary assessment of data including bronchoalveolar lavage (BAL), evidence of immune dysregulation and longitudinal disease behaviour on and off therapy. However, the guidelines do not support this process, giving HRCT too decisive a role while discounting observed disease behaviour (see also the article entitled, "Challenges in the classification of fibrotic ILD" by Bendstrup *et al* in this issue of Sarcoidosis Vasc Diffuse Lung Dis and "The revised ATS/ERS/JRS/ALAT diagnostic criteria for idiopathic pulmonary fibrosis (IPF) – practical implications" by Wells in Respiratory Research 2013;14[Suppl 1]:S2) (8,10) and minimising the role of BAL. Furthermore, the "multidisciplinary" diagnosis described in the guidelines includes only surgical and radiological information, and does not account for input from a clinician. While the guidelines contain valuable recommendations, updates based on consensus agreement to facilitate definitive diagnosis in more patients are urgently needed.

REAL-WORLD MANAGEMENT ISSUES

Risk-benefit considerations of surgical lung biopsy

As noted, SLB is indicated for patients with suspected IPF in whom HRCT fails to show a definite UIP pattern (1). However, biopsy is not without risk and cannot be performed in approximately 50% of patients. In patients with severe disease, the decision to perform lung biopsy is essentially a risk–benefit balance, since risk increases and prognostic value diminishes as DL_{CO} falls below 30–35% (11). Video-assisted thoracoscopic surgery (VATS) is generally very well tolerated, with a low (<2%) risk of infection (12). The major complications of SLB are acute exacerbation of IPF, acute lung injury, prolonged air leak, readmission for pneumothorax, haemorrhage, and pain.

Risk factors for mortality among patients undergoing VATS include multiple comorbidities, more severe dyspnoea, a higher respiratory rate, a lower PaO_2, a higher $PaCO_2$, a $PaCO_2/PaO_2$ index of ≥0.72, preoperative dependence on oxygen therapy, and pulmonary hypertension (13-15).

A DL_{CO} <35% predicted and an idiopathic UIP pattern (as opposed to UIP associated with collagen vascular disease) have also been shown to predict mortality in these patients (16). The largest study on mortality and risk factors of SLB in idiopathic interstitial pneumonias (IIPs) included 140 IPF, 46 NSIP, and 16 COP patients (17). This retrospective study showed that 4.3% of patients died within 30 days after surgical biopsy. There was no difference in mortality between VATS or OLB, and no difference between IPF and other IIPs. DL_{CO} was the best predictor of mortality: patients with a DL_{CO} <50% had a mortality of 11% vs 1.4% in those with DL_{CO} >50%. Acute exacerbation at the time of biopsy is another established risk factor for mortality (17). Patients undergoing VATS should be forewarned that there is a small risk of conversion to open thoracotomy.

In a retrospective study of 73 patients undergoing diagnostic SLB, the complication rate was 16% and 30-day mortality was 2.7%. A definite

histopathologic diagnosis was obtained in 81% of the patients, with UIP being the most common diagnosis (31%). Interestingly, the clinical diagnosis changed following biopsy for 73% of patients, and resulted in changes in treatment in 53% of patients (18).

The major downside of lung biopsy is that the surgery itself, or associated procedures such as general anaesthesia and positive pressure ventilation, can result in an accelerated decline of lung function. It is hypothesised that in a subset of patients with IPF, surgical lung biopsy may trigger an exacerbation or cause acute lung injury (19). Patients with low DLCO (<50% predicted) had higher mortality and complication rate than the high DLCO group (20). Moreover, a DLCO <35% of predicted and idiopathic usual interstitial pneumonitis (versus usual interstitial pneumonitis associated with collagen vascular disease) were predictors of mortality in an earlier Mayo Clinic series (21).

Staging

"Staging" is a method of measuring the severity of specific, well-defined diseases, such as IPF and many types of cancer (22). Staging defines discrete points in the course of individual diseases that are clinically detectable, reflect severity in terms of risk of death or residual impairment, and possess some clinical significance for prognosis and choice of therapeutic modality (22). Applying staging criteria in IPF has yielded some useful information about prognostic features which inform therapeutic management (eligibility for lung transplant as an example). However, there remain grey areas in our understanding of the disease, which make it difficult to definitively categorise each patient.

The 2011 IPF guidelines list several features that are associated with an increased risk of mortality, including both baseline factors (e.g., severity of dyspnoea, extent of honeycombing) and longitudinal factors (e.g., increase in dyspnoea, worsening of fibrosis) (1).

For staging disease, the guidelines have proposed the use of terms such as "mild", "moderate" and "severe", with the proposed stages reflecting a combination of features such as resting pulmonary function test measurements and/or extent of radiologic abnormalities. However, the parameters separating each of the three stages are somewhat unclear, given that the natural history of IPF is not well defined and disease course is variable.

Three broad disease courses have been identified: slowly progressive disease; rapidly progressive disease; and progressive disease with episodes of acute exacerbations (Figure 1) (23). While certain features are known to be associated with increased mortality, it is not clear whether the presence of one of more of these features identifies a subpopulation of patients with "advanced" or "end-stage" IPF.

There is a clear influence of the disease staging concept on the 2011 labelling of pirfenidone (Esbriet) in Europe, which states that the drug is indicated for the treatment of "mild-to-moderate IPF" (24). However, "mild-to-moderate" is not explicitly defined in the label or the guidelines. It is assumed rather to refer to the inclusion criteria of the population in clinical trials (4). These were forced vital capacity (FVC) ≥50% predicted, DL_{CO} ≥35% predicted and 6-minute walk distance ≥150 m. Subsequent clinical experience and the recent (2014) terms of licensing of pirfenidone and nintedanib in the USA, as well as nintedanib in Europe, in which there is a straightforward indication for the treatment of IPF, suggest the "mild-to-moderate" construct may not be particularly relevant in directing anti-fibrotic prescribing decisions (25,26). Indeed, assessment and guidance of patient eligibility for pirfenidone and duration of treatment in cases of progression has been found to be variable across European countries (27).

A number of clinical features have been found to have prognostic value in IPF. FVC is clearly predictive of clinical outcome: both baseline FVC and the change in FVC over time are significantly correlated with mortality (5,28). Similarly, 6MWD is significantly correlated with mortality both cross-sectionally and longitudinally (29). Other features have also been shown to predict mortality, albeit with suboptimal specificity, such as dyspnoea score, combined physiologic index (CPI) and alveolar–arterial oxygen gradient (30).

To improve specificity, several prognostic factors may be combined into a composite risk score. Examples include "ROSE", which incorporates the Medical Research Council dyspnoea score, 6MWD and CPI (30); the score developed by du Bois et al, which includes age, respiratory hospitalisation,
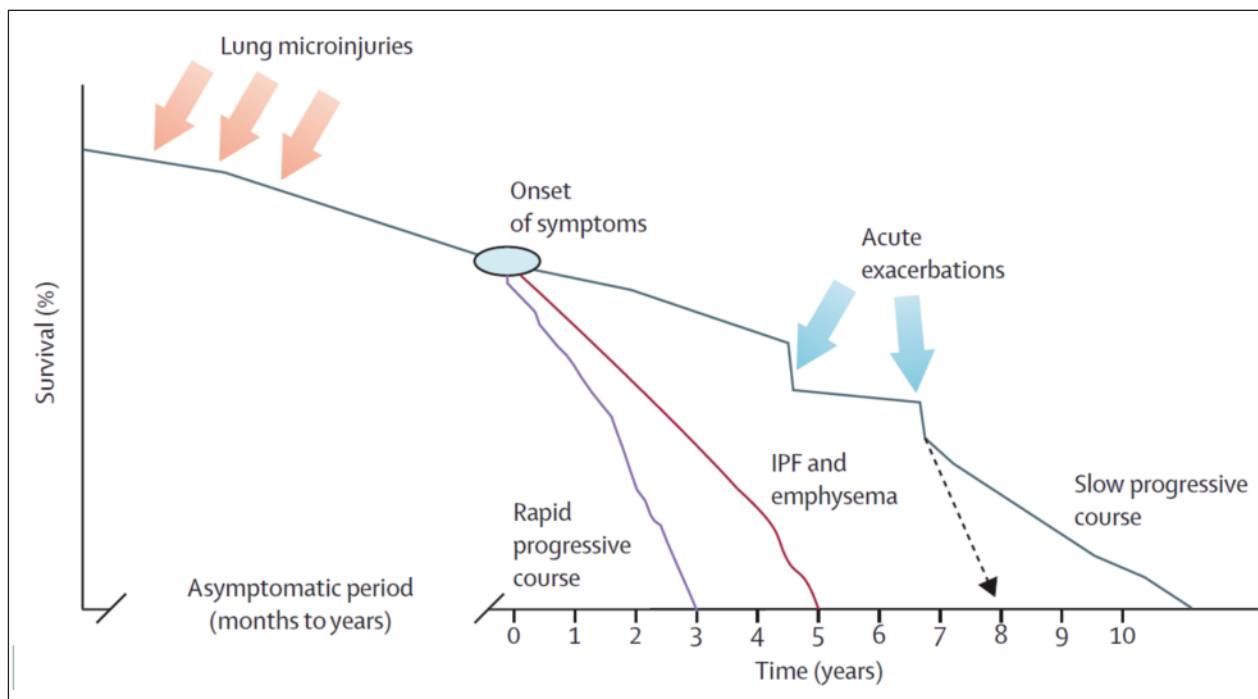
Fig. 1. Clinical phenotypes of IPF (23). The heterogeneous natural history pattern in patients with IPF. The disease has a long (months to years) asymptomatic period. Patients consult when the severity of the lung lesions reaches a threshold that is enough to provoke symptoms. Most patients follow a relatively slow clinical and functional decline (slowly progressive) after diagnosis. About 10% of these patients present with episodes of acute clinical deterioration (acute exacerbations) that precede and possibly initiate the terminal phase of their disease. A few patients have a short duration of illness with a rapidly progressive clinical course. Heavy smokers might develop pulmonary fibrosis combined with emphysema, with shorter survival compared with patients with IPF alone. IPF=idiopathic pulmonary fibrosis

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FVC% predicted, and 24-wk change in FVC (28); and the GAP Index, which relies on gender, age, FVC and diffusion capacity (2).

The GAP Index allows patients to be classified into one of three stages (I, II and III) based on their GAP Index scores (Figure 2). Mortality differs significantly by stage, from 5.6% at 1 year for those with stage I disease (0–3 points) to 39.2% in those with stage III disease (6–8 points) (2).
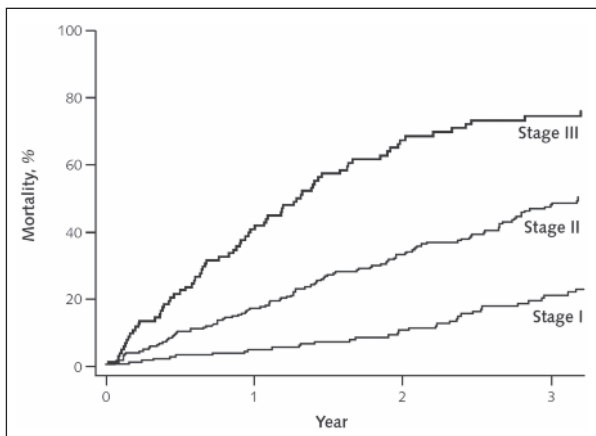
Maintaining clinical benefit

Pirfenidone and nintedanib have been proven to slow disease progression in IPF patient populations. Compared to placebo, nintedanib patients were found to have a lower risk of first acute exacerbation while patients taking pirfenidone achieved a 48% reduction in risk of all-cause mortality (24,26). Although adverse events associated with anti-fibrotics can affect adherence compromising ongoing clinical

benefit, these reactions tend to be predictable and are, for the most part, manageable.

Pirfenidone

The most commonly reported adverse reactions in patients receiving the recommended dose of pirfenidone were nausea (32.4%), rash (26.2%), diarrhoea (18.8%), fatigue (18.5%), dyspepsia (16.1%), anorexia (11.4%), headache (10.1%), and photosensitivity reaction (9.3%) (24).

To reduce the incidence of nausea and dizziness, it is recommended that pirfenidone tablets are swallowed whole with water and taken with food. Taking the capsules in split doses rather than simultaneously has been suggested to help reduce side effects (31). If symptoms persist despite this advice, the dose may be reduced to 1–2 capsules (267–534 mg) 2–3 times/day with food and then re-escalated to the recommended daily dose if tolerated (24).

Fig. 2. GAP Index and Staging System (2)

Patients who experience a mild-to-moderate photosensitivity reaction or rash should be reminded to use a sunblock daily and to avoid sun exposure. The dose of pirfenidone may be reduced to 3 capsules/day (1 capsule three times/day). If the rash persists after 7 days, pirfenidone should be discontinued for 15 days and then re-escalated to the recommended daily dose. Patients who experience severe photosensitivity reaction or rash should stop treatment and seek medical advice. Once the rash has resolved, pirfenidone may be re-introduced at the discretion of the physician (24).

Of note, an expert panel of clinicians specialising in IPF has recently developed detailed consensus recommendations on the management of adverse events related to pirfenidone (31).

Nintedanib

Like pirfenidone, nintedanib should be taken with food to reduce gastrointestinal toxicity. The most common adverse reactions to nintedanib were diarrhoea (62%), nausea (24%), abdominal pain (15%), liver enzyme elevation (14%), vomiting (12%), decreased appetite (11%), weight loss (10%) and hypertension (5%) (27).

Patients who experience adverse reactions may require symptomatic treatment, if applicable, as well as dose reduction or temporary interruption of treatment. Once adverse reactions have resolved, nintedanib may be resumed at full dosage (150 mg twice daily) or at the reduced dosage (100 mg twice daily), which subsequently may be increased. In patients who cannot tolerate 100 mg twice daily, nintedanib treatment should be discontinued (27).

FUTURE PERSPECTIVES

While our understanding of IPF has increased markedly over the past few years and, with the introduction of pirfenidone and nintedanib, we have succeeded in the slowing of progression in a disease that was previously regarded as being virtually untreatable, IPF nonetheless continues to present many challenges. As noted, there is currently much research being conducted in the field of IPF and a number of emerging trends may help in the management of IPF in the future.

Cryobiopsy

Transbronchial lung cryobiopsy (TBLC) is a promising new diagnostic technique that may one day become a viable alternative to SLB (32). According to the protocol developed at the Ospedale GB Morgagni, Forlì, Italy, TBLC is performed under general anaesthesia using a rigid tracheoscope and fiberoptic bronchoscope plus a Fogarty balloon to control bleeding. Once in position, a 2.4 mm cryoprobe is placed at a perpendicular angle approximately 10 mm from the thoracic wall and cooled for 5–6 seconds. The specimens obtained are typically 5–6 mm long.

It is likely that the risk of pneumothorax will decline as pulmonologists and centres become more experienced with the technique. As experience and confidence grows, it is possible that TBLC may eventually replace SLB in the evaluation of suspected IPF.

Genetics/biomarkers

Genetics are believed to play an important role in the pathophysiology of IPF (33). The strongest evidence for a genetic component comes from patients with familial pulmonary fibrosis, which may

be defined as two or more members of the same biological family affected by some form of pulmonary fibrosis (1). To date, mutations have been identified in patients with familial pulmonary fibrosis in genes that encode telomerase components (TERT and TERC) and proteins involved in surfactant metabolism (e.g., SFTPC, SFTPA2, SFTPB, ABCA3, TITF1) (34-37).

Several gene variants are known to be associated with susceptibility to lung fibrosis, the best known of which is a common promotor polymorphism (rs35705950) in the *MUC5B* gene. This variant is present in around 38% of patients with IPF or familial pulmonary fibrosis versus just 9% of controls (38). Carriers of the mutation show increased expression of MUC5B, a protein required for defense against infection in the airways (39).

Based on the current data, genetic screening may be appropriate for a subgroup of patients with pulmonary fibrosis; namely, those with familial fibrosis (irrespective of lung pathology), telomeropathy, aged under 50 years, and pre-lung transplantation. Screening should be offered to family members in order to allow early detection of lung disease and associated disorders and for an opportunity to give advice about avoiding potentially noxious agents. Although there are currently no specific treatments for patients with telomerase or surfactant mutations, this is an active area of drug development and agents are likely to become available in the future.

While personalised (or precision) medicine (the selection of monotherapies on the basis of individualised biomarker signals) has had excellent results in therapeutic areas such as oncology, it is not expected to play a major role in the near future of IPF management. There is currently no robust biomarker available to guide treatment in IPF (40). Because multiple co-activated pathways are involved in the pathogenesis of IPF, targeted therapies are unlikely to work well in isolation. Furthermore, personalised medicine essentially relies on a treatment being highly specific for a particular form of a disease – yet both pirfenidone and nintedanib are pleiotropic drugs, with multiple targets and effects. Personalised medicine is therefore unlikely to be useful in routine management of IPF in the medium-term future due to the complex nature of the disease pathogenesis (41).

Challenges in future trial design

While the availability of effective therapies is a major advance, it also raises important questions about the future design of clinical trials and how to optimise treatment in clinical practice.

In the phase III trials of pirfenidone and nintedanib, the primary endpoint was the change in FVC. These trials were powered based on an expected FVC decline of around 220 ml/year (based on declines in placebo arms in previous trials), of which 30–40 ml/year is due to normal ageing and the remaining 180 ml/year is due to disease. For ethical reasons, future trials are unlikely to include a placebo control and the investigational drug or therapeutic strategy will need to improve upon the new standard of care. Investigational therapies will most likely be studied in add-on protocols – i.e., given in combination with pirfenidone or nintedanib – which in turn will herald the use of combination regimens in clinical practice (41). These trials will need to be powered based on an anticipated FVC decline of approximately 110 ml/year in patients in the control arm receiving pirfenidone or nintedanib. Alternative primary endpoints may also be recognised.

Sequential and combination therapy

In the near future, sequential treatment is likely to be the default option. Patients will most likely be started on either pirfenidone or nintedanib and then switched to the alternative drug when initial therapy either stops working (although clear criteria for treatment failure have not yet been outlined) or cannot be tolerated. At present, no recommendation can be made regarding the choice of initial drug or optimum duration of therapy before switching because it is not known how long the treatment effects of pirfenidone or nintedanib endure. While there are preliminary clinical data suggesting long-term effects of pirfenidone up to 7 years in a patient subgroup, there are no long-term data for nintedanib, which was approved in the USA in October 2014 and in Europe in January 2015 (42,43). It is also unclear whether either drug is efficacious as a second-line therapy (41).

In the intermediate future, the management of IPF will likely involve combination regimens, as has been the case in other chronic lung diseases. Many

potential therapeutic targets have been identified, the most promising of which are LOXL2, interleukin-4, interleukin-13, connective tissue growth factor, $\alpha v \beta 6$ integrin and NOX4 (41). An important consideration when developing combination regimens will be to ensure that the novel drug complements the therapy to which it is added. Combination therapy with pirfenidone and nintedanib is beyond the scope of this short discussion.

Conclusion

Despite progress in recent years, many unanswered questions and challenges remain in our understanding and management of IPF. Guidelines need to be updated to include management strategies for patients with probable/possible IPF, biopsy needs to be accessible to more patients and staging could be clearer and treatment management improved. Fortunately, there is much on the horizon that gives us cause for optimism. Developments such as cryobiopsy, an ever-increasing understanding of the role of genetic factors, novel treatment targets and strategies all have the potential to address current challenges in IPF as we move into the future.

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