Idiopathic Pulmonary Fibrosis: An Update

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Introduction

Interstitial lung disease (ILD) refers to a broad spectrum of lung conditions that affect the interstitial rather than the airway compartment of the lung. It spans a large number of distinct entities, but can be viewed broadly as those with an identifiable cause, those with granulomatous pathology and those considered idiopathic interstitial pneumonias. The age of onset varies considerably. The most common chronic progressive-fibrosing idiopathic interstitial pneumonia is idiopathic pulmonary fibrosis (IPF)(Lederer and Martinez, 2018). Significant progress has been made in the understanding and management of IPF in recent years. This article will outline an update on IPF.

Epidemiology

Epidemiological data for IPF varies due to differing methods of data collection worldwide. Throughout Europe and North America, the estimated incidence of IPF ranges from 2.8 to 19 cases per 100,000 people per year (Olson et al., 2018). Prevalence of IPF increases with age, with the majority of patients age over 50 years at diagnosis. Patients are typically in the sixth and seventh decades of life at presentation. Patients with IPF who are younger than 50 at diagnosis are rare. Such patients may have familial IPF or may subsequently manifest features of an underlying connective tissue disorder that was sub-clinical at time of first presentation. The condition is more common in males than females.

Pathogenesis

The pathogenesis of IPF is unclear but likely results from the dynamic interaction of genetic, epigenetic, and environmental risk factors. Genetic predisposition results from gene mutations (e.g. MUC5B polymorphism) or a combination of common gene variants. Known environmental exposure includes cigarette smoke and viruses. Micro-aspiration of gastric contents in to the lung is another potential cause of injury, with the prevalence of gastro-oesophageal reflux being elevated in IPF (Raghu et al., 2006). A number of aging-associated mechanisms have been implicated, including genetic instability, abnormal shortening of telomeres, mitochondrial dysfunction and cellular senescence. This results in abnormal phenotypic and functional changes in the airway and alveolar epithelium. The activated dysfunctional epithelium releases mediators, leading to the migration, proliferation and activation of hyperactive mesenchymal cells. These organise in clusters of fibroblasts and myofibroblasts, which are responsible for the secretion of excessive extracellular matrix materials, including collagens and fibronectin. This leads to profibrotic macrophages arriving and progressive matrix stiffness, ultimately resulting in lung destruction (Pardo and Selman, 2021).

Clinical presentation of IPF

Shortness of breath on exertion is typically the first presenting feature of IPF. It presents insidiously, with gradual progression over a period of months to years. Patients can notice reduced exercise tolerance. A persistent dry cough is another presenting feature, along with weight loss and fatigue. Initial symptoms are often attributed to ageing, deconditioning or other co-morbidities, which may lead to a delayed diagnosis for patients. IPF patients may have non-specific symptoms for up to five years before a diagnosis is made. Common mis-diagnoses include chronic obstructive pulmonary disease (COPD) and congestive cardiac failure (CCF) (Hewson et al., 2018).

Fine end-inspiratory crepitations on clinical examination are a common finding in IPF patients. These ‘velcro-like’ crepitations are predominantly audible in the lower posterior lung zones and in the axillae. Crepitations are the most specific among the chest physical signs at first presentation (Martinez et al., 2017). Finger clubbing is also found in 30-50% of patients. . As the disease progresses and respiratory failure develops, central cyanosis may be evident.

The lack of specific clinical features and co-existence of other conditions can delay the diagnosis of IPF, which has a negative impact on patient survival in IPF (Lamas et al., 2011). Increased awareness and knowledge of interstitial lung diseases will be required to improve early diagnosis and earlier access to treatments.

Investigations

A chest x-ray is a very useful first radiological test when a patient presents with symptoms of dyspnoea and cough. It is important to note that the chest x-ray lacks diagnostic specificity for IPF but is useful to exclude other causes of dyspnoea. The appearances may be normal or demonstrate non-specific findings early in the disease course of IPF. As IPF progresses, the hallmark chest x-ray findings are reduced inspiratory lung volumes, bilateral reticular opacification, with a basilar and peripheral predilection/predominance.

In IPF, pulmonary function tests will demonstrate a restrictive abnormality. This is evident by reduced lung volumes, as identified by a total lung capacity (TLC) measurement of less than 80% predicted. The forced vital capacity (FVC) is typically reduced, along with reduced diffusing capacity of the lung for carbon monoxide (DLCO), indicating impaired gas exchange. However, it is important to remember that spirometry and lung volume measurements can be normal, particularly during the early stages of disease or when there is concurrent emphysema (Cottin et al., 2017).

If an interstitial lung disease is suspected from the history, physical examination and initial investigations, a high-resolution CT (HRCT) thorax should be performed. The HRCT thorax will determine if ILD is present and can identify specific radiological patterns that will help the clinician in narrowing the differential diagnosis (Raghu et al., 2018). The finding of honeycombing with or without peripheral traction bronchiectasis in a subpleural and basal distribution is consistent with definite ‘usual interstitial pneumonia’ (UIP), considered the hallmark radiological pattern of IPF. The positive predictive value of a radiologic diagnosis of UIP on a HRCT scan for a pathological diagnosis of UIP is between 90 – 100% (Raghu et al., 2018). Mediastinal lymphadenopathy may be present in patients with UP and asymmetric disease can occur in up to 25% of cases.

Making a diagnosis

A major challenge in making a diagnosis of IPF is the exclusion of other known causes of ILD, such as environmental exposures, connective tissue disorders and drug toxicity. A detailed history of both medication use and exposures at home, work and other places the patient frequently visits is required. Clinicians are required to make judgements regarding the aetiological significance of a patients exposures. Careful attention to a thorough physical examination excluding other

The National Patient Charter for IPF

This charter informs patients of the six key areas of care that they should be entitled to:

1) Early and accurate diagnosis

2) Clear information about IPF

3) Access to medication and oxygen

4) Access to pulmonary rehabilitation and exercise programmes

5) Early referral to the national lung transplant unit with a minimal emphasis on age

6) Access to psychological and palliative care services.

Taken from: https://irishthoracicsociety.com/wp-content/uploads/2018/08/ITS-Pulmonary-Fibrosis-Position-Statement.pdf

clinical signs of connective tissue disorders is also required.

To establish a diagnosis of IPF and to rule out other ILD's or overlapping conditions, cases require multi-disciplinary team (MDT) discussion, ideally at ILD specialist centres. A diagnosis of IPF is achieved through an iterative discussion within the MDT, a practice that is endorsed by international guidelines (Raghu et al., 2018).

Management

As with other chronic lung conditions, management of IPF patients involves improving symptoms, preserving lung function, improving health quality, minimising adverse effects of treatment and ideally, improving survival. (Martinez et al., 2017).

Pharmacological management

Two anti-fibrotic drugs were approved for IPF treatment in 2014, namely pirfenidone and nintedanib, based on well-conducted randomised controlled trial, which demonstrated that both drugs slowed disease progression.

Pirfenidone (Esbriet™) is an anti-fibrotic drug that decreases the proliferation of fibroblasts and the accumulation of collagen. It reduces the rate of decline in the FVC, with improved progression-free survival (King Jr et al., 2014). It should be taken three times daily with food at a target dose of 801mg that is titrated upwards over a 14 day period. Liver function tests are required at baseline and regularly thereafter. Side effects include photosensitivity, rash, and gastrointestinal discomfort. Patients are advised to avoid sun exposure and to wear sun protection. If side effects and/or hepatotoxicity develops, the dose of pirfenidone can be reduced, or temporarily held and reintroduced at a slower dose titration. Pirfenidone is metabolised by the cytochrome P450 1A2 (CYP1A2) enzymes, and should be avoided or used with extreme caution if the patient is also using other CYP12A inhibitors (e.g. ciprofloxacin) or inducers (e.g. omeprazole).

Nintedanib (Ofev™) is a tyrosine kinase inhibitor, with inhibition of platelet-derived growth factor (PDGF) receptor, fibroblast growth factor (FGF) receptor, and vascular endothelial growth factor (VEGF) receptor. It reduces the rate of decline in FVC and reduces the time to the first acute exacerbation of IPF (Richeldi et al., 2014). It has also demonstrated efficacy across a broad range of progressive fibrosing ILD's, in addition to IPF (Flaherty et al., 2019). The dose of nintedanib is 150mg orally twice daily. Liver function tests are required at baseline and regularly thereafter. Side effects include diarrhoea and nausea. Due to the mechanism of action of nintedanib, patients on oral anti coagulation should be treated with nintedanib if the anticipated benefit outweighs the risk and they should be closely monitored for bleeding risk.

Choosing one anti-fibrotic over another can be difficult for the clinician, due to the absence of head to head clinical trials. Decisions about anti-fibrotics should be based on what is most suitable for the individual patient.

A number of trials have provided evidence that the combination of pirfenidone and nintedanib is safe and tolerable to patients (Flaherty et al., 2018). Future randomised controlled trials to evaluate whether combining the two anti-fibrotic drugs increases effectiveness remains to be determined. At present, the drugs are not given in combination.

Non-pharmacologic

Non-pharmacologic management is essential. This includes cessation of smoking, maintaining an up to-date vaccination profile, diagnosis and management of anxiety and depression, weight and nutrition management (Lederer and Martinez, 2018)

Pulmonary rehabilitation is a comprehensive intervention designed to improve the physical and psychological status of patients with chronic advanced lung disease through respiratory muscle and exercise training. It also promotes long-term adherence to health-enhancing behaviours. Pulmonary rehabilitation for IPF patients increases exercise tolerance and quality of life (Gomes-Neto et al., 2018).

The evidence base for long-term oxygen therapy (LTOT) in IPF is lacking. Patients with significant resting hypoxemia (oxygen saturation <88% or PaO2 < 7.3 kPa) should be treated with LTOT. Many patients with IPF have normal oxygen saturations at rest but rapidly desaturation upon exertion. The use of ambulatory oxygen when mobilising may improve exercise capacity and relieve dyspnoea in these patients. However, the burden of therapy and the potential to generate anxiety about running out of oxygen must be considered. More studies regarding the role of oxygen therapy in IPF are required.

Whilst micro-aspiration of gastric contents into the lung has been implicated in the aetiology of IPF, antacid therapy has failed to demonstrate any benefit and in fact, may be associated with increased respiratory infections (Kreuter et al., 2016). Thus, reflux-directed therapy should be considered on an individual basis if the patient has symptoms of reflux.

Patient support and education are essential when a patient receives a diagnosis of IPF. The Irish Lung Fibrosis Association (ILFA) is the national patient organisation for lung fibrosis, providing support to patients and their families. Exercise DVD's, '2000 steps a day' challenges and regular patient support groups are some ways that ILFA provides support and education. The National Patient Charter for IPF was developed by ILFA in 2015 (SEE IMAGE TWO). Once a diagnosis of IPF is suspected, there is a need to deliver the key areas of this charter to improve patient care and outcomes.

Monitoring a patient over time/ disease response

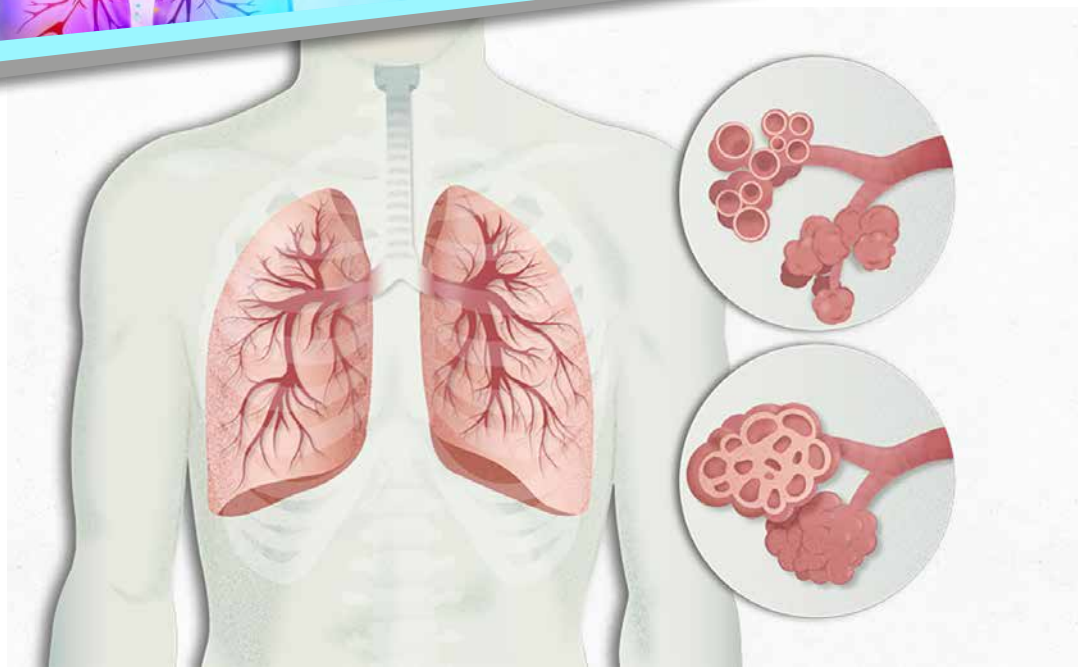
Once a patient is diagnosed and commenced on appropriate therapy, regular review at specialist ILD clinics is necessary. Symptoms are closely monitored. Patients are advised that whilst the anti fibrotic drugs should slow the rate of FVC decline, their symptoms will persist and likely worsen. PFT's are performed at regular intervals. Longitudinal changes in respiratory physiology is an important predictor of mortality in IPF (Nakamura and Suda, 2015). A decline in FVC over six to twelve months is a reliable predictor of mortality in IPF. DLCO declines are also associated with decreased survival, but demonstrate less consistency than the FVC (Latsi et al., 2003).

Assessment for lung transplantation

Lung transplantation is recognised as the only effective treatment for IPF. In Ireland over 30% of patients receiving lung transplantation have IPF. Appropriate and timely referral to the National Lung Transplant Centre at the Mater University Hospital is required. All patients should be considered for transplant referral with clear emphasis on prioritising patients with rapidly declining lung function, DLCO below 40%, or respiratory failure. Older patients frequently have co-morbidities that preclude transplantation but decisions should be made on a case by case basis (Walsh and O'Regan, 2018).

Concurrent rates of cancer in IPF

Patients with IPF have increased rates of lung cancer, with the prevalence of lung cancer in IPF varying from 4.4 to 9.8% (Margaritopoulos et al., 2017). This is particularly in those



who have a smoking pack year history of at least 35 pack years and those with co-existing emphysema (Kato et al., 2018). Lung cancer commonly develops in the peripheral parts of the lower lobes, adjacent to areas of UIP. Distinction between malignancy and areas of confluent fibrosis can be difficult, especially if prior imaging is unavailable. Clinicians should be mindful of the increased rates of lung cancer in IPF.

Palliative care

Patients with IPF should receive timely and adequate access to community, general and specialist palliative care services. The major aims of palliative care in IPF are to improve quality of life by addressing the patients symptoms. Their psychological and spiritual needs can also be explored, to ensure that IPF patients live well with their disease.

IPF continues to have a poor prognosis. International studies demonstrate a median survival of three to five years from diagnosis. However, the prognosis is variable with some patients experiencing longer survival times dependent on the disease stage.

Acute exacerbations (flares) of IPF

Whilst the majority of IPF patients demonstrate a gradual worsening in their symptoms over time, a significant minority of patients experience episodes of acute worsening of respiratory symptoms without an identifiable cause, termed an acute exacerbation of IPF (Collard et al., 2016). An acute exacerbation of IPF is most likely triggered by an acute event (e.g. micro-aspiration, infection, mechanical stretch) on a background of fibrosis, leading to widespread acute lung injury (characterised by hyaline membrane formation and interstitial oedema). The acute exacerbation may also precipitate acceleration of the underlying fibrotic process (Collard et al., 2016).

There are no proven effective therapies for acute exacerbations of IPF. Many patients receive systemic steroids without an evidence base to support this intervention. Supplemental oxygen is given to correct hypoxemia. Estimated in-hospital mortality is up to 90% in IPF patients presenting with an acute exacerbation and in respiratory failure. Mechanical ventilation carries a high mortality rate. If there is no clear reversible cause for the respiratory failure outside of the progressive fibrosis, it is not recommended to place a patient on mechanical ventilation (Rush et al., 2016). Non-invasive respiratory support, such as non-invasive ventilation and nasal high flow oxygen therapy can be delivered as the ceiling of care.

Conclusion

The knowledge around IPF has greatly expanded over the past ten years. Optimal management involves early diagnosis via MDT input and deciding on appropriate treatment. Management decisions involve balancing standard-of-care approaches with the patients' wishes and expectations. Treatment requires consideration of medication side effects, potential drug interactions, consideration of the optimal time for lung transplant assessment and recognising when it may be appropriate to withdraw intervention and introduce palliative care measures. More studies are required to assess the optimal treatments for acute exacerbations of IPF and to develop optimal therapies to halt and even reverse progressive fibrosis.

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