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The management and treatment of idiopathic pulmonary fibrosis: dawn of a new era

The theme of this edition of Respiratory disease in practice is idiopathic pulmonary fibrosis (IPF), a condition that is devastating for patients and their families, and very challenging for healthcare professionals, but where there have recently been significant improvements in both the treatment and management of the condition.

Many reading this journal will have cared for patients with IPF, the most common form of interstitial lung disease and a condition that causes very significant morbidity and mortality. It is more prevalent than many fatal cancers, with around 5,000 deaths each year in the UK, and has a median survival of less than five years from diagnosis. Patients receiving this diagnosis often have significant symptoms, particularly progressive cough and breathlessness, can struggle to access support services including palliative care and, until recently, have been told that there are probably no effective treatments for their condition. This landscape has, however, changed dramatically over the last year or two. As described in this issue, a licensed drug that slows disease progression is now available to some patients with IPF, with other promising compounds undergoing clinical trials. A new structured approach to the delivery of specialist services is also being developed, to allow access to new treatments and to provide expert symptom management and support for patients.

Diagnosing IPF

Patients with IPF typically present to their primary care practitioner with cough and breathlessness, are found to have an abnormal chest X-ray and are then referred to local respiratory medicine services. A priority is to make a firm diagnosis of IPF, as opposed to other forms of interstitial lung disease or other cardiorespiratory disease. With the designation of regional specialist centres, of which there are currently 18 in England and Wales, the diagnosis can be confirmed by referral to the regional specialist centre’s multidisciplinary team (MDT) who can review clinical information and high-resolution computerised tomography (CT) scans to either confirm a diagnosis or, occasionally, recommend a surgical lung biopsy for further diagnostic information. Once the diagnosis of IPF is established, a patient’s eligibility for treatment can be assessed, together with their suitability for lung transplant referral and for inclusion in clinical trials of newer agents.

Treating IPF

In the past, many patients with IPF would receive immunosuppressive drugs, with regimes incorporating corticosteroids and a steroid-sparing agent, such as azathioprine. However, these have been shown to be ineffective in slowing disease progression and should no longer be prescribed. Importantly, the recent ASCEND trial showed that a NICE-approved drug, pirfenidone (Esbriet), was able to slow the rate of lung function decline in IPF patients and, when the data was combined with data from the previous CAPACITY trials, there was also evidence of a reduction in mortality. While these results suggest disease progression is slowed rather than halted or reversed by pirfenidone, this represents a major advance for IPF patients. Other drugs in the pipeline also offer novel anti-fibrotic strategies, including nintedanib and other compounds, such as anti-IL-13. A future challenge will be working out the relative merits of the different drugs and their place, alone or in combinations, in treatment algorithms.

Currently, in the UK, pirfenidone is the only licensed drug for treatment of IPF and may be prescribed by specialist centres for patients with progressive disease, subject to a confirmed diagnosis and to specific lung function criteria. Careful follow-up of these patients by the specialist centres is required, ideally in a shared-care partnership with local physicians as many IPF patients find it difficult to travel to appointments. These arrangements, together with pharmacist input, will allow targeted prescribing of other drugs as they become available, building expertise in how to use these drugs and in providing support to patients.

Caring for IPF patients

The MDT is vital in making the diagnosis of IPF, starting specific treatment where appropriate and providing ongoing support to patients. Beyond disease-specific treatment, patients require robust management of gastro-oesophageal reflux and assessment for supplemental oxygen, and are likely to benefit from pulmonary rehabilitation. Other services, including palliative care, can also input into symptom control. Specialist nurses make valuable contributions to the service and their liaison with primary care and other support available locally can make a real difference to patients, who typically are elderly and may have significant co-morbidities.

Conclusion

In conclusion, patients receiving a diagnosis of IPF should now have access to specialist advice and services on a regional basis and, in many cases, to treatment for their condition. These represent important steps on a journey towards effective management and improved quality of care in this challenging disease.

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Declarations of interest

The author has declared that their institution has previously received honoraria or grant funding from InterMune UK and Ireland for research, service support or participation at advisory boards.

References

New data in IPF: a pivotal change in the future of IPF treatment

The past decade has seen a rejuvenated interest in basic science research and clinical therapies for idiopathic pulmonary fibrosis (IPF); however, a number of potential therapies have had disappointingly negative results.1-6 There has been a paucity of treatments that can affect disease pathogenesis and thus prognosis. Coupled with this, the PANTHER trial resulted in a paradigm shift in the management of patients with IPF, with the perceived standard of care, triple immunosuppressive therapy, showing a significantly higher mortality rate compared to placebo.7 In the remaining two arms of the study, N-acetylcysteine did not show any benefit in patients with IPF.8 This left respiratory physicians with a difficult patient discussion, with the limited options of palliation of symptoms, or lung transplantation in highly selected patients. However, hope is not lost, for clinicians and patients alike, as recent therapeutic advances have provided a new dawn in the therapeutic era of IPF.

New treatments

Pirfenidone, an anti-fibrotic agent, is the only licensed treatment in Europe for mild to moderate IPF. The two CAPACITY7 phase three randomised controlled trials (RCT), paved the way for the European license after demonstrating a statistically significant 2.5% absolute and 22.8% relative reduction in the decline of forced vital capacity (FVC) and improved progression free survival at 72 weeks in pooled data.9 These trials, however, highlighted the difficulties posed by the heterogeneity in clinical course and response to treatment in patients with IPF, in that only one of the two trials reached its primary endpoint. This cast some skepticism among clinicians on the efficacy of pirfenidone in IPF and resulted in a negative response from the United States Food and Drug Administration (US FDA), leading to the development of a further randomised controlled trial of pirfenidone in IPF (ASCEND). The recent publication of the ASCEND trial10 has made a major contribution to dissipate these concerns and has been pivotal in reinforcing the utility and benefit of pirfenidone for the management of patients with mild to moderate IPF. The publication of two phase three trials of an investigational and unlicensed therapy, nintedanib, an intracellular inhibitor targeting multiple tyrosine kinases, in IPF (INPULSIS™-1 and -2)11, have provided an additional breakthrough in the therapeutic management of IPF.

The ASCEND trial10 met its primary end-point showing that pirfenidone treatment resulted in a statistically significant reduction in the decline of FVC at one year. This corresponded with a reduced decline in distance walked on the six-minute walk test. The proportion of patients who had a greater than 10% decline in FVC, a predictor of mortality in IPF, or death, was also significantly lower in the pirfenidone group compared with the placebo group with a relative difference of 47.9% (46 (16.5%) vs 88 (31.8%)). Similarly, the proportion of patients that did not decline was higher in the pirfenidone group (63 (22.7%) vs 27 (9.7%) in the placebo group). Disappointingly, but not unexpectedly, when both placebo and treated patients continued to decline, there was no effect on breathlessness. In a pre-specified mortality analysis requested by the FDA, combining the one-year data for CAPACITY and ASCEND there was a statistically significant reduction in all-cause and IPF-related mortality at year one with pirfenidone treatment (Table 1).

In the INPULSIS trials11 the annual rate of change in FVC over one year was significantly lower in the nintedanib group versus placebo. Similarly, the proportion of patients with an FVC decline of less than 5%, denoted as a response to treatment, was statistically higher in the nintedanib group compared with placebo in both trials. When a less than 10% cut off was used for response to treatment, this was statistically higher in the nintedanib group compared with placebo in INPULSIS-1 but not INPULSIS-2. A pre-specified pooled analysis of the primary end point showed a significant reduction in the decline of FVC (109.9 ml difference) and a greater proportion of both definitions of a response to treatment in the nintedanib group compared with placebo. Time to first exacerbation, i.e., the proportion of people with at least one investigator reported exacerbation and improvement in symptoms, varied between the two trials, with no significant difference between the nintedanib and placebo groups observed in the pooled data. These trials were not powered to detect statistically significant differences in mortality.

Differing adverse effects were reported in the ASCEND and INPULSIS trials, these included gastrointestinal effects, which were common in both trials and skin manifestations, which were more frequently reported in the ASCEND trial. Adverse events were tolerated in both trials, despite what appeared to be a high incidence of diarrhoea and serious adverse events in the INPULSIS trials.

So, as respiratory physicians, what does this mean for our IPF patients?

The publication of three randomised controlled clinical trials of differing therapies in IPF represents a long awaited paradigm shift in the management era of IPF.

One needs to be cautious about comparing the ASCEND and INPULSIS trials as they differed in their design, centralised review of diagnosis and recruitment criteria. Patients in both these clinical trials represent a ‘pure’ cohort of patients with IPF, as comorbidities are excluded. We should therefore be mindful about extrapolating these results to patients that fall

Table 1. Mortality in the pooled CAPACITY and ASCEND trials

<table>
<thead>
<tr>
<th>Death, no. (%)</th>
<th>Pirfenidone</th>
<th>Placebo</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause</td>
<td>22 (3.5)</td>
<td>42 (6.7)</td>
<td>0.52 (0.31–0.87)</td>
<td>0.01</td>
</tr>
<tr>
<td>IPF-related</td>
<td>7 (1.1)</td>
<td>22 (3.5)</td>
<td>0.32 (0.14–0.76)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

CI=confidence interval
outside of the recruitment criteria. These results provide limited insight into the use of these drugs in patients with more severe disease, or those with co-existing comorbidities such as emphysema.

**Conclusion**

Despite these cautions, from a patient and clinician perspective it is exciting that not one, but two treatments have shown a reduction in lung function decline, together with clinical data from the licensed treatment for IPF (pirfenidone), which demonstrated a significant mortality benefit. These trials will serve as a catalyst to future basic science research and clinical trials of new emerging treatments, in the much needed hunt for early diagnosis and ultimately a cure for this devastating disease.

**Declaration of interest**

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**References**


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**From diagnosis through treatment: the vital role of the clinical nurse specialist in the management of patients with IPF**

Idiopathic pulmonary fibrosis (IPF) is a rapidly progressing interstitial lung disease with high rates of morbidity and mortality. The management of IPF requires a multidisciplinary team (MDT) approach, with regular monitoring and evaluation. The IPF specialist nurse is a vital member of the MDT together with specialist respiratory physicians, radiologists, pathologists and a coordinator. The specialist nurse has a key role in assessing and implementing both the pharmacological and non-pharmacological pathways of care, in order to help patients palliate their symptoms and optimise their quality of life.

The IPF specialist nurse provides an anchor for patients while going through the diagnostic process. They are the patient advocate at the MDT meetings and implement the chosen care pathway, thereafter. Nurses are also crucial in providing best supportive care, which should be tailored to disease severity and rate of progression, and patient preferences from diagnosis through to end-of-life care.

**Management of treatment**

Pirfenidone can now be considered the standard of care in the UK for the treatment of patients with mild and moderate IPF. This means the IPF specialist nurse has a particularly important role in managing patients who are taking this medication, which is associated with both gastrointestinal and skin-related side effects and which requires additional monitoring. Pirfenidone delays gastric emptying, its effect being related to peak blood levels, which are substantially reduced by taking the drug with food. Monthly liver function monitoring is part of the licence requirements for the first six months of treatment, and three monthly thereafter. These hospital visits are an opportunity for the nurse to provide support and encouragement to the patient. Few patients believe that photosensitivity is a problem in the UK, but it is in reality. Nausea and loss of appetite are less predictable but are dose limiting symptoms in some patients, particularly the very thin, in whom slow titration can be of benefit. All these side effects can be managed by slow titration and regular telephone support, either locally and/or by the IPF care telephone support service.

**Symptom management**

The focus of nursing care then falls to the management and palliation of breathlessness, cough, exercise induced hypoxia and anxiety, in order to preserve quality of life. Patients want information, access to centres of excellence and truth from the team caring for them. Regular evaluation of lung function, hypoxia and the 6-minute walk test in particular, will enable timely introduction of ambulatory oxygen so patients can continue to lead active lives. There is controversy as to the timing of pulmonary rehabilitation, but there is evidence that it does help, albeit for a limited time, and should definitely be recommended when patients stop leaving the house, before they become housebound. It is well documented that the management of breathlessness is best provided by a MDT, with the aim to empower patients to control their breathing. Management includes education, fan therapy, structured anxiety management and physiotherapy, all of which have been shown to be helpful.

Cough is a debilitating symptom for many IPF patients. Its
cause is complex, although it is thought that cough receptors are more sensitive in IPF patients and this, together with gastric reflux, may well be contributing to this menacing symptom. Managing cough is difficult; stopping patients smoking, the use of anti-reflux therapy, codeine and opiates are all useful.

**Psychological support**

The emotional impact of having IPF can lead to a number of psychological problems, which broadly manifest as anxiety and depression. Guidelines for the management of anxiety and depression recommend psychological treatment, pharmacological treatment or both in combination. We have nursing evidence demonstrating efficacy of a brief (six-session) cognitive behavioural intervention in chronic obstructive pulmonary disease. As a nurse, it is important to routinely assess the psychological needs of patients. Nurses need to explore the concerns of the patient, gain insight into their coping strategies, acknowledge their losses, support, guide and signpost patients either to formal psychological support, or help and guide patient-directed goal setting. A cognitive behavioural therapy approach can help patients understand the ways in which their thoughts and feelings about breathlessness affect the way they deal with their symptoms.

Good communication skills are key to managing IPF patients whose disease trajectory is uncertain. Nurses can use predictors of mortality, age, 24-week reduction in forced vital capacity, diffusing capacity of carbon monoxide, change in quality of life and number of hospitalisations, to open timely discussions of advanced care planning and palliation. Initiating these discussions is challenging but essential, in order to provide information around expected health deterioration; these discussions should be carefully delivered, to allow the patient to remain optimistic, especially towards the end of their life.

**Conclusion**

In summary, access to specialist interstitial lung disease nurses is essential to this group of patients. They provide the anchor during the diagnostic pathway, monitor the patient during the early phase, provide the bridge to community services and offer continuity of care for the patient. Specialist nurses need to offer regular monitoring of the patient, and assess and share care with community palliative teams early. The importance of the nursing role demonstrates the need for earlier referral to specialist centres with MDTs, so that patients can get access to this crucial care as early as possible in their treatment pathway.

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**References**

Idiopathic pulmonary fibrosis (IPF) is a progressive disease of the lung interstitium, previously known as cryptogenic fibrosing alveolitis in the UK. The median survival time for patients with IPF is less than five years from diagnosis.\(^1\) Previously used corticosteroid and immunosuppressive treatment regimens have been shown to be ineffective.\(^2\) In 2011, guidelines did not recommend any therapy for this condition.\(^3\) However, over the last few years research has led to some potentially effective therapies, including pirfenidone\(^4\) and nintedanib.\(^5\) Currently, only pirfenidone is licensed in the UK for the treatment of mild and moderate IPF. This research has raised the profile of IPF and its treatment.

This article is written from the perspective of a general respiratory centre, i.e., without a specialist multidisciplinary team (MDT) for IPF. Colchester Hospital University Foundation Trust covers a population of almost 400,000 in northeast Essex. This includes a coastal retirement strip with a high proportion of elderly patients, an urban area and a number of rural villages, extending 30 miles inland. The data on the incidence of IPF is incomplete for our district, but we currently have 43 patients on our database.

**Referral**

Patients are referred to the general respiratory clinic by four main routes. Patients referred directly from primary care often have a history of chronic cough with a non-diagnostic chest x-ray. This makes up between a quarter and a third of referrals to the chest clinic. A further quarter of patients are referred via the lung cancer pathway, with a suspicious chest x-ray that has lead to a computerised tomography (CT) scan, which has excluded lung cancer but suggested interstitial lung disease. Some patients come from general hospital admissions. In over 80% of these referrals the admitting team have initially considered congestive cardiac failure as a diagnosis. In our elderly population these two diagnoses can co-exist. A further quarter of patients are referred by other means: from the community based chronic obstructive pulmonary disease (COPD) team via the COPD MDT, from other specialists or as incidental findings on routine radiology.

The patients referred are frequently elderly and referred late in the course of their illness, and IPF is often only considered when other diagnoses have been rejected. In common with many UK district general hospitals, our informatics structure could be improved, and we struggle to keep a registry of all of our IPF patients due to a lack of staff and resources.

With an ebb in the evidence for corticosteroids and immunomodulating drugs for IPF, the thrust of our management has been side effect limitation, usually by tapering or stopping corticosteroids. The most that our patients could hope for is N-acetylcysteine, prescribed directly from our clinic because it is not available in community pharmacies in our area. Now the evidence for this has waned following data published in 2014.\(^6\)

It is therefore completely game changing for our patients that an effective treatment option is available for IPF in the form of pirfenidone.

**What does this mean for respiratory physicians in non-specialist centres?**

For physicians in general respiratory centres this represents a huge change in our practice. In the UK, the arrival of a treatment option for IPF has coincided with an organisational change within the NHS. The use of pirfenidone was agreed by NICE in 2013 and in time they will likely also pass judgment on nintedanib. These drugs are firmly within the remit of new specialised commissioning, and for the NHS this will mean that the drugs will only be available for patients attending hospitals with a catchment area of over one million in population. The stated ambition of this process is to ‘bring equity and excellence to the provision of specialist care’.

For our patients in district hospitals it will mean a programme of early referral to specialist respiratory clinics, so that early IPF can be identified and appropriately treated. However, general respiratory physicians face a number of challenges in relation to early referral. These include the fact that, at present, the bulk of our patients are at, or below, the forced vital capacity 50% predicted cut off before they are referred to us. In addition, our informatics are woefully under
resourced so we are only able to run registries of patients using personal resources. Patients may also be reluctant to travel the distances required to the specialised commissioning centres.

The new treatment option for patients with IPF will also increase referrals to district general hospitals at a time when we are struggling to deal with the increase in referrals of patients with lung malignancy via the cancer pathways. Specialist commissioning arrangements will make referral to specialist centres necessary at an earlier stage of the disease process if initiation of the new treatments is to occur in a timely fashion. In order to ensure that IPF patients have access to treatment and specialist care, new referral strategies will need to be put in place for commissioning at both a specialist centre and district general hospital level.

**Key points from this issue**

Idiopathic pulmonary fibrosis is the most common form of interstitial lung disease and causes significant morbidity and mortality. Until recently, there have been no effective treatments for this condition.

Pirfenidone is currently the only licensed treatment in the UK for the treatment of IPF. In clinical trials, pirfenidone has been shown to reduce lung function decline and demonstrated a significant mortality benefit.

Access to an MDT is essential for patients with IPF. As part of this team, specialist nurses have a key role in assessing and implementing both the pharmacological, and non-pharmacological, pathways of care in order to help patients palliate their symptoms and optimise their quality of life.

In order for patients with IPF to have access to new treatments and specialist care, new referral strategies will need to be put into place.
A big step forward for IPF patients

The first and only licensed treatment proven to slow disease progression¹

A novel oral agent with anti-fibrotic effects¹,²

Effective in reducing decline in lung function¹,³

Generally well tolerated⁴

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