Idiopathic pulmonary fibrosis is an incurable condition and has a poor prognosis: treatment aims to alleviate patients’ symptoms, improve their quality of life and slow disease progression

Idiopathic pulmonary fibrosis management

By Lloyd Mayers, ClinDipPharm, MRPharmS, and Patricia Ging, MSc, MRPharmS

Patients with an interstitial lung disease, such as idiopathic pulmonary fibrosis (IPF), have complex management needs. These include: home and ambulatory oxygen therapy; referral for lung transplantation; pulmonary rehabilitation; diagnosis and management of pulmonary hypertension; and psychosocial support. This care is best delivered by specialists and is driving the commissioning of specialist interstitial lung disease centres in the UK — bringing together the expertise needed for prompt and accurate diagnosis of IPF and for provision of ongoing care to patients at a regional level.

Although IPF is uncommon, pharmacists are likely to encounter patients with the condition, or other interstitial lung diseases, in primary care, hospital or community; understanding the principles that underpin its management will help demystify this condition and enable pharmacists to support patients with IPF.

IPF is predominantly defined by fibrosis and there is little, if any, active inflammation. The radiological pattern of fibrosis represents a common endpoint of many different conditions and this can confuse the prognosis and management of patients with interstitial lung disease.

Given that IPF is typified by architectural destruction of the lung parenchyma, pharmacological cure — even if resolution of fibrosis could be achieved — is not possible; therefore, current treatment strategies are directed at ameliorating disease progression, preventing exacerbations, managing symptoms and improving quality of life.

Limitations of current evidence

Clinical trials in IPF have typically involved relatively small patient populations with diverse baseline characteristics, such as disease severity and the use of immunosuppression, which is now thought to be harmful in IPF (see Box 1, p226). Rates of disease progression in IPF, even among patients with similar baseline characteristics, are unpredictable; therefore it is difficult to ensure treatment groups are matched appropriately to demonstrate an affect of a medicine.

Surrogate endpoints, including changes in forced vital capacity (FVC) and exercise tolerance, that are typically used in IPF studies have not yet been demonstrated to translate into improved survival or quality of life in these patients.

Pirfenidone

Pirfenidone, the only licensed treatment for IPF, has recently been approved by the National Institute for Health and Care Excellence for use by patients with an FVC between 50% and 80% of predicted and a diffusing capacity of the lung of more than 40% predicted. The
mechanism of action of pirfenidone is unclear but it appears to have anti-inflammatory, antioxidant and antifibrotic properties. European approval was based on the outcome of the CAPACITY trials, which demonstrated a dose-dependent reduction in the rate of FVC decline. Although there was a trend towards reduced mortality, the studies were not powered sufficiently to assess this. The ASCEND study, which is currently ongoing, will further clarify the efficacy of pirfenidone.

The most common adverse effects associated with pirfenidone treatment include:

- Fatigue
- Transient dizziness, which might interfere with activities requiring alertness and co-ordination
- Nausea and dyspepsia (reduced when pirfenidone is taken with food)
- Photosensitivity reactions, including severe sunburn, rashes, pruritus and dry skin — the likelihood of photosensitivity rash, which can be severe, is unpredictable and all patients should be counselled on avoiding sun exposure and on the need to use suncream during treatment

Uncommonly, abnormalities of hepatic function can occur, but these will usually resolve when treatment is discontinued temporarily. Depending on the degree of dysfunction it may be possible to restart pirfenidone after liver function tests have returned to normal. Liver function tests should be monitored monthly for the first six months and quarterly thereafter.

Pirfenidone is titrated slowly over three weeks: starting with 267mg three times a day the dose is increased weekly to 801mg three times a day. Patients who experience nausea, dyspepsia or dizziness can titrate their dose at a slower rate or take a lower dose. Taking pirfenidone with food can also reduce the occurrence of side effects.

Pirfenidone is predominantly metabolised by the cytochrome P450 isoenzyme CYP1A2, and to a lesser extent by CYP2C9, CYP2C19, CYP2D6 and CYP2E1, into inactive metabolites that are excreted by the kidneys. Pirfenidone can be prescribed for patients with mild-to-moderate hepatic or renal impairment with caution; dose

---

**Box 1: Immunosuppression**

Immunosuppression with corticosteroids plus or minus a steroid-sparing medicine (eg, azathioprine or cyclophosphamide) was once considered standard care for patients with idiopathic pulmonary fibrosis (IPF). Although the evidence to support it was lacking, the British Thoracic Society and American Thoracic Society guidelines, published in 1999 and 2000 respectively, recommended prednisolone and azathioprine for IPF.

In 2005, the observation that levels of the antioxidant glutathione were lower than normal in the lungs of patients with IPF led to the IFIGENIA study, in which researchers investigated the effect of adding N-acetylcysteine (NAC) to standard treatment with prednisolone and azathioprine. Oxidative stress was proposed to have a role in the development of the condition and because NAC contains a sulphhydryl group it acts as an antioxidant; it also breaks down to provide cysteine, which is required for the synthesis of glutathiones. Researchers reported that adding oral NAC to treatment regimens preserved forced vital capacity and diffusing capacity of the lungs more than dual therapy alone. Subsequent guidelines gave differing recommendations: the BTS supported triple therapy but the ATS did not — albeit both rather weakly.

In 2008, the PANTHER-IPF study was started to investigate immunosuppression for patients with mild-to-moderate IPF. Patients were assigned to one of three treatment arms. These were:

- Triple therapy, ie, azathioprine, prednisolone and NAC
- NAC monotherapy
- No treatment (placebo)

The rates of hospital admission, death and serious adverse drug reactions were significantly higher for patients on triple therapy than for those on placebo and these rates were consistent with those seen in the IFIGENIA study. The triple therapy arm was discontinued after the interim analysis revealed that immunosuppression was doing more harm than good, probably as a result of an increased incidence of infections and exacerbations. The comparison of NAC with no treatment has not yet been published.

Revised guidelines, including those from the National Institute for Health and Care Excellence, now strongly advise against the use of immunosuppression in the management of IPF.
reductions are not required unless side effects are experienced. Pirfenidone is not recommended for patients with severe hepatic disease or renal impairment (creatinine clearance under 30ml/min).

Fluvoxamine, a potent enzyme inhibitor, and grapefruit juice should be avoided during treatment with pirfenidone. Amiodarone, ciprofloxacin, propafenone, fluconazole, fluoxetine and paroxetine can be prescribed with caution but may increase the likelihood of adverse effects — a lower dose of pirfenidone may be required.

Hepatic enzyme inducers, such as rifampicin, can reduce levels of pirfenidone and should be avoided. CYP1A2 is theoretically induced by omeprazole, therefore, patients receiving treatment for gastro-oesophageal reflux disease should be prescribed an alternative proton pump inhibitor. Patients who smoke should be encouraged to quit because smoking is known to induce the isoenzyme CYP1A2.

Pirfenidone does not appear to interfere with the metabolism or clearance of other medicines.

N-Acetylcysteine

Although immunosuppressants are no longer recommended for patients with IPF (see Box 1), the role of oral N-acetylcysteine (NAC) in the absence of immunosuppression has yet to be clarified. The placebo and oral NAC arms of the PANTHER-IPF study are ongoing and results are due to be published this year. NAC, prescribed at 600mg three times a day, is still widely used in IPF and is recommended as an option by NICE.7

Although NAC is available as a nutritional supplement, it is not licensed as a medicinal product in the UK and is often procured as an unlicensed product. Similarly to other mucolytics, it can cause gastrointestinal disturbances and damage the gastric mucosa — causing gastritis, ulcers or upper gastrointestinal bleeding. NAC can chemically react with some medicines; some antibiotics are inactivated by NAC and so patients are normally advised to withhold treatment when taking oral antibiotics.

Other treatment options

Some evidence suggests that the endogenous peptide endothelin-1 — which is involved in the development of pulmonary hypertension — contributes to the development of fibrosis in IPF. Numerous multicentre studies have investigated the use of the endothelin receptor antagonists ambrisentan,7 bosentan8,9 and macitentan10 to modify disease progression in IPF; however, results have been disappointing and these medicines are not recommended.11 Results from clinical trials investigating the use of interferon, imatinib, colchicine, anticoagulants and antivirals are also disappointing.

Although the endothelin antagonists appear to have no place in modifying disease progression in IPF, up to 60% of patients with severe IPF have concomitant pulmonary hypertension.12 This comorbidity can increase some of the clinical symptoms of IPF, such as breathlessness, hypoxia and exercise intolerance. Patients with concomitant pulmonary hypertension should be referred for assessment by a specialist centre.

Non-pharmacological care is described in Box 2.
Patients should be advised to lose weight, eat healthily (avoiding precipitating dietary factors, eg, alcohol, coffee, chocolate and fatty foods) and stop smoking. NICE recommends treating IPF patients who have gastro-oesophageal reflux disease according to existing NICE guidelines for dyspepsia. However, because gastro-oesophageal reflux disease is often asymptomatic (around 40% of people affected) it is common practice for treatment to be started at the time IPF is diagnosed. Although there are no evidence-based regimens for this, some clinicians favour an aggressive approach, incorporating a proton pump inhibitor, an H₂ receptor antagonist and a prokinetic. Given the lack of evidence, burden of polypharmacy and risk of QTc prolongation with some prokinetics, this regimen should not be used routinely; treatment with a single medicine, such as a proton pump inhibitor, may be sufficient.

Cough Cough can be a particularly distressing symptom for patients with IPF and it can affect quality of life considerably. Although chronic cough with IPF may be associated with reflux or post-nasal drip, there appears to be a distinct “IPF-cough” that is frustrating for patients and difficult to treat.13

The treatment options for cough in IPF are anecdotal: opiates, antirrhinics and nebulised local anaesthetics, eg, lidocaine, have all been used with varying degrees of benefit. The loss of airway sensation and gag reflex with the use of nebulised local anaesthetics can be distressing for patients and increases their risk of aspiration — patients should not eat or drink for at least two hours after administration.

Although there is some evidence that suggests corticosteroids ameliorate the cough response, safety concerns associated with the use of corticosteroids in IPF limit this approach. Based on the results of a small case series14 and a randomised controlled trial,15 thalidomide is recommended by NICE as an option for intractable IPF-associated cough.16 Thalidomide is teratogenic; therefore, a pregnancy prevention programme must be adhered to when prescribing and supplying the drug. Side effects of thalidomide include constipation, drowsiness and neuropathy. The risk of neuropathy appears to be dose-dependent and can be severe and irreversible; therefore, thalidomide is generally reserved for patients who have an IPF cough that is disabling, is severely affecting their quality of life and has not responded to other therapies.

There has been research conducted recently into the use of gabapentin for non-IPF chronic cough and daily doses of 1,800mg were effective and tolerated well.17 Although there is no evidence to support the use of gabapentin in IPF, it is occasionally tried in patients before considering thalidomide.

**Pipeline**

It is now understood that there is considerable variability in IPF phenotype (affecting the rate of progression, severity of associated symptoms and the frequency and severity of exacerbations) and response to treatment. In the future, it is likely that IPF management will be guided by physiological parameters of disease severity and genetic markers — in a model similar to the current approach to cancer therapy.

Nintedanib (BIBF-1120) is a mixed function tyrosine kinase inhibitor that acts on numerous pathways proposed to be involved in pulmonary fibrosis. The TOMORROW trial18 has demonstrated that for patients treated with nintedanib there is a trend towards a reduction in lung function decline and fewer exacerbations compared with patients treated with placebo. Side effects include gastrointestinal upset and hepatic dysfunction.

Two parallel studies are due for completion towards the end of the year; if these support the findings of the TOMORROW study then nintedanib is likely to become available as a treatment option for IPF in the next 12 to 18 months.

**References**