Nintedanib for treating idiopathic pulmonary fibrosis

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Idiopathic pulmonary fibrosis (IPF) is the most common form of interstitial lung disease. It is a chronic progressive condition associated with significant morbidity and mortality. In the UK, 5000 new cases of IPF are diagnosed each year and the incidence is rising (Navaratnam et al, 2011). IPF is associated with poor prognosis and the median survival from diagnosis is between 2.9 and 5 years (Bjoraker et al, 1998). This has, in part, been related to an absence for many years of therapies that can effectively impact the natural history of IPF.

Over the last five years there has been much cause for optimism in the management of IPF, with the introduction of two novel antifibrotic therapies—pirfenidone and more recently nintedanib. This article will discuss the recent publication of the National Institute for Health and Care Excellence (NICE) technology appraisal guidance for *Nintedanib for Treating Idiopathic Pulmomary Fibrosis* (NICE, 2016) and discuss its impact on patients and physicians.

The story so far

A decade ago the horizon appeared bleak. What was considered the standard of care in managing IPF with triple therapy using prednisolone, azathioprine and N-acetylcysteine (NAC), was disbanded due to an excessive mortality rate on treatment (Idiopathic Pulmonary Fibrosis Clinical Research Network et al, 2012). For many years this left the only treatment options of palliative and supportive measures for all patients, and lung transplant in highly selective cases.

Hope was not lost—enter pirfenidone, a novel antifibrotic and anti-inflammatory agent designed to inhibit fibroblast activity. In the pooled analysis, two randomised control trials (RCTs), CAPACITY-1 and CAPACITY-2 (Noble et al, 2011), demonstrated that patients taking pirfenidone had less decline in their forced vital capacity (FVC) at 72 weeks (8.5% vs. 11% for placebo), and significantly fewer patients reached a decline of 10% predicted FVC, considered a prognostic marker in IPF. Pirfenidone received NICE approval in April 2013 for IPF patients with an FVC of 50–80% predicted (NICE, 2013).

A subsequent primarily USA-based phase 3 RCT (ASCEND) (King et al, 2014) further strengthened the case for pirfenidone use in IPF by showing similar significant reduction in FVC decline, a lower proportion of patients having a 10% decline in predicted FVC (relative difference of 49.7%; 46 (16.5%) vs. 88 (31.8%)) and significantly more patients showing no decline in FVC (63 (22.7%) vs. 27 (9.7%)), in the pirfenidone group compared to placebo.

A pre-specified pooled analysis of CAPACITY and ASCEND demonstrated a significant reduction in all-cause and IPF-related mortality with the use of pirfenidone (hazard ratio 0.52 and 0.32 respectively).

Nintedanib: Future hope

Nintedanib is a tyrosine kinase inhibitor, which causes intracellular inhibition of growth factor receptors, which are believed to be involved in the fibrotic process (Wollin et al, 2014).

Two phase-three RCTs—the INPULSIS 1 and INPULSIS 2 trials (Richeldi et al, 2014)—demonstrated a significant reduction in the rate of decline in FVC with the pre-specified pooled analysis showing the annual rate of decline to be approximately half in the nintedanib group (113.6ml vs. 223.5ml) compared to placebo.

Sub-analysis using a definition of a decline in FVC percent predicted of less than 10% as a 'response' to therapy, found that a significantly greater proportion of patients taking nintedanib (70.1%) responded to treatment compared to placebo (60.5%). Although these studies were not powered to detect differences in mortality, there was a trend towards a reduction in mortality associated with the use of nintedanib. The results failed to show a consistent reduction in the number of acute exacerbations with nintedanib.

NICE recommendations

Following the publication of the INPULSIS trials in addition to a phase IIb study, the TOMORROW trial (Richeldi et al, 2011), NICE have undertaken a technology appraisal looking at the use of nintedanib in IPF (NICE, 2016). Similar to pirfenidone,

nintedanib has been recommended for use in patients with an FVC of 50–80% and must be discontinued in patients who demonstrate a decline in percent predicted FVC of 10% or more in a 12-month period—this represents something of a double-edged sword.

While the approval nintedanib has received from NICE is clearly welcome, data from the British Thoracic Society (2015) registry and our own data (Chaudhuri and Leonard, 2014) demonstrate that up to 35–40% of patients have an FVC greater than 80% at presentation and have significant disease both symptomatically and radiologically. Patients may have pre-morbid FVC values, that are greater than 100% due to normal population variation or associated smoking history, and so a decline in lung function to 80% may represent significant deterioration, and have impact on the development of progressive breathlessness and cough.

In addition, the INPULSIS trials indicated that nintedanib is equally effective in patients where baseline FVC of greater than 80% is predicted. As things stand, there is no disease-modifying therapy on offer for a significant proportion of patients with IPF who have an FVC of greater than 80% predicted.

The only management that can be offered to this 'lost' group of IPF patients is recruitment into clinical trials if available, or the unsatisfactory period of watching patients lung function decline and symptoms progress before we can offer them any disease-modifying treatment that has a potential to impact mortality.

What does this mean to patients and physicians?

Pirfenidone and nintedanib have similar impact on lung function, so how do patients choose between the two? Patient choice and informed shared decision-making between health care professionals is imperative. Although critics may question the validity of the pre-specified pooled analysis, pirfenidone may have an edge, as it is currently the only treatment to show a statistical mortality benefit.

Physicians must also take co-morbidities into consideration, as pirfenidone is contraindicated in renal failure and nintedanib is contraindicated in patients with peanut allergy, significant cardiovascular risk, or those taking dual anti-platelets or warfarin.

Patients may also choose due to life style considerations such as pill burden (two tablets a day for nintedanib vs. 6-9 tablets for pirfenidone) and factors such as the risk of the differing side-effect profile on the two treatments. Pirfenidone is most commonly associated with nausea (36%), rash (28%), diarrhoea (22%), fatigue (21%), and a photosensitivity reaction (12%) (King et al, 2014). Nintedanib is frequently associated with diarrhoea (62%) and nausea (24%) (Wollin et al, 2014). Some patients may spend a lot of time outdoors and not like the thought of having to wear sunscreen with pirfenidone, and others may prefer to risk nausea and lethargy over diarrhoea and loose stools with nintedanib.

The biggest impact of the NICE approval of nintedanib is patient choice. This is an exciting and dynamic time to be involved in managing patients with IPF. There are now two therapeutic options that impact disease progression, and many more therapies in the pipeline undergoing clinical trials. The future of IPF management is moving in a positive direction. BJHCM

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