

Position Statement from the Irish Thoracic Society on the treatment of Idiopathic Pulmonary Fibrosis

BACKGROUND

Idiopathic Pulmonary Fibrosis (IPF) is a rare, chronic and fatal disease characterised by progressively worsening respiratory function [1,2]. Since the publication of the Interstitial Lung Disease Guideline from the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society in 2008 [3], some significant new information has emerged which will alter the therapeutic management of Irish patients diagnosed with IPF.

1. Firstly, the approval in February 2011, by the European Medicines Agency of the anti-fibrotic drug pirfenidone as the first licensed treatment for IPF [4] and secondly, the publication indicating that the triple therapy utilised in the PANTHER trial, comprising of N-Acetylcysteine, azathioprine and prednisolone was discontinued due to excessive deaths, hospitalisations and adverse events compared to placebo [5]. This combination is used by some physicians treating IPF in Ireland. In order to ensure that physicians and patients are appropriately guided on the most up to date information to manage complex respiratory conditions, the Irish Thoracic Society has felt it prudent to produce a position statement on this issue as clinical guidelines may not be updated for some time. In recognition of these issues and other medical treatments competing for scarce resources the Irish Thoracic Society Interstitial Lung Disease (ILD) Group proposes the following approach to IPF and its treatment in Ireland. The ITS ILD group recognises the need to take a proactive responsible position and advise the HSE in regards to IPF treatments

2. The group proposes the formation of a national network of multidisciplinary teams composed of respiratory, radiology, and pathology consultants with a particular expertise in IPF. This network will provide support to respiratory consultants in the diagnosis and management of IPF, in particular atypical cases.
3. Designated IPF Centres

In recognition of the current financial environment and the complexities that IPF patients face we propose a network of designated IPF centres across the country. These centres would be based on the presence of:

- a) Designated physician with specific expertise in IPF from a critical mass of 3 physicians.
- b) Radiologist with specific expertise in ILD,
- c) Thoracic surgery on site ,
- d) On site Pathologist with specific expertise ,
- e) Nurse specialist,
- f) Rehabilitation services

These centres would provide support and access to other respiratory consultants who wish to refer patients with IPF for further management. It is envisaged that new treatments would be delivered from these centres in an attempt to optimise access and delivery. The patient will be subject to a shared care arrangement with continuing involvement and monitoring by the referring centre.

4. POSITION REGARDING HSE PIRFENIDONE SUBMISSION

Over the last two decades, a large number of clinical trials of promising medicines have failed to demonstrate any benefit in improving outcomes in IPF subjects. The recent approval of Pirfenidone (Esbriet®) to treat mild to moderate IPF in adults has been a significant advancement in the management of IPF. Results from two large, pivotal, international, placebo controlled, randomised clinical trials [6] along with supporting data from two Japanese clinical trials [7,8] with pirfenidone were submitted to the European Medicines Agency. Although there were variations in trial outcomes, these four studies showed a beneficial effect on the rate of decline of pulmonary function over 72 weeks. The value of pirfenidone in improving progression free survival has been demonstrated in a meta-analysis by the Cochrane Collaborative [9]. Although the drug was well tolerated with high rates of compliance, pirfenidone can be associated with adverse events including raised hepatic enzymes and photosensitivity reactions. These shall require monitoring and patient support to ensure optimal benefit to patients.

The ITS ILD group recommends:

- IPF patients being considered for this therapy and newer treatments should be managed and treated in designated centres with the support of a multidisciplinary team.
- Patients who have been diagnosed with mild to moderate IPF (based upon a baseline Forced Vital Capacity of <80% - >50%) should be offered treatment with pirfenidone and a Dlco > 35%. The benefits and risks should be discussed prior to commencing treatment.
- Patients with evidence of airflow obstruction defined as a FEV1/FVC ratio of <0.7 would be excluded

- For patients who have been commenced on pirfenidone, a registry of patient outcomes under the auspices of the ITS would be maintained.
- Supporting clinical staff and nurses should be trained on pirfenidone and how to support patients on therapy.
- Other forms of Interstitial Lung Disease (ILD) that are not IPF, or advanced IPF should not be considered for treatment with pirfenidone.
- Patients with significant co morbidities should not be considered for pirfenidone

5. POSITION REGARDING THE USE OF TRIPLE THERAPY

It is difficult to know the true extent of triple therapy (N-Acetylcysteine, azathioprine and prednisolone) use in the Irish IPF population due the lack of a centralised registry of treatment. None the less, the recent PANTHER publication has the potential to cause physicians and patients a degree of uncertainty, particularly for patients who are established on triple therapy. Further data on the trial is due to be published later in 2012 with full results expected in 2013.

1. The BTS ILD SAG recommends that new patients with definite IPF should NOT be initiated on a regimen containing prednisolone plus azathioprine
2. No concerns have been raised as a result of preliminary analysis of the n-acetylcysteine monotherapy arm of the study. The preliminary announcement by the NHLBI has no immediate implications on the use of NAC in IPF
3. 'In patients with definite IPF already receiving combination prednisolone/azathioprine/n-acetylcysteine therapy, it is recommended that azathioprine therapy in particular should be withdrawn if there is evidence of disease progression (declining lung function). In patients

established on triple therapy with 'stable' disease, the decision to withdraw should be on a cases-by-case basis, but the threshold for withdrawing azathioprine from elderly patients should be low.

4. Patients with fibrotic ILD that is not definite IPF (e.g, NSIP, HP) should continue to be managed according to clinical judgement and the BTS ILD Guidelines.

Ratified by the ITS – Nov 2012

[1] American Thoracic Society/European Respiratory Society. *Am J Respir Crit Care Med* 2002;165:277-304;

[2] Raghu G et al. *Am J Respir Crit Care Med* 2011;183:788-824; 3. Collard HR et al. *Am J Respir Crit Care Med* 2003;168:538-42

[3] Bradley B, Branley HM, Egan JJ, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008;63(Suppl 5):v1e58.

[4] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002154/WC500102979.pdf (accessed 7th March 2012)

[5] Prednisolone, Azathioprine and N Acetylcysteine for pulmonary fibrosis. *N Engl J Med* 2012; 366; 1968-77

[6] Noble PW et al. *Lancet* 2011;377:1760-9

[7] Azuma A et al. *Am J Respir Crit Care Med* 2005;171:1040-7;

[8] Taniguchi H et al. *Eur Respir J* 2010;35:821-9.

[9] Spagnolo P et al. *The Cochrane Library* 2010; Issue 9

[10] [http://www.brit-thoracic.org.uk/guidelines/interstitial-lung-disease-\(dpld\)-guideline.aspx](http://www.brit-thoracic.org.uk/guidelines/interstitial-lung-disease-(dpld)-guideline.aspx)

(accessed 7th March2012)