Therapeutic protocol for idiopathic pulmonary fibrosis

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Idiopathic pulmonary fibrosis (IPF) is a chronic irreversibly progressive fibrosing lung disease of unknown etiology leading to death all patients affected with a reported median survival of 3 years post diagnosis[1,2]. Five year survival of IPF patients is estimated at 30%, much worse than that of many common neoplasms such as breast and prostate cancer and similar to that of lung cancer[3]. The need for appropriate management and treatment of IPF patients appears imperative and urgent due to the high mortality rate of the disease. Up to now the only therapeutic approach proved to increase survival was lung transplantation[1,2].

The therapeutic strategy with triple combination with steroids, azathioprine and n-acetyl cysteine proved harmful for the treatment of IPF patients as shown by the interim analysis of the **PANTHER** trial that demonstrated significant increase of the risk of death, hospitalizations, exacerbations and other major complications at the treated group compared to the placebo arm of the study[4]. Based on the above mentioned data, triple therapy is not recommended anymore in many European countries, such as France, Germany, the Netherlands, Austria, Sweden, the United Kingdom, Denmark and Ireland.

On the other hand, since 2011 the European Medical Agency (EMA) has approved of **pirfenidone** (Esbriet) as the only up to now treatment for the management of IPF patients. In October 2014, pirfenidone (Esbriet) obtained official authorization for use in IPF patients by FDA approval in the United States of America as well. In Greece "Esbriet" is characterized as an orphan drug coming under the provisions of paragraph 12§2 of the law N.3816/2010 and belongs to the category B of the Ministry Decision Y.A.28822/08.04.2014. More precisely, pirfenidone has obtained circulation authorization for the treatment of IPF both from EMA [indication: mild/moderate IPF, that is Forced Vital Capacity (FVC) ≥50% predicted and Diffusing capacity of the lung for carbon monoxide ($DLCO_{SB}$) ≥35% predicted] and by the FDA (IPF independently of severity status, that is for mild/moderate and severe disease).

Pirfenidone is a drug with anti-fibrotic, anti-inflammatory and anti-oxidative properties proven to slow down the progression of the disease. The main phase III trials for pirfenidone (**CAPACITY and ASCEND**) demonstrated that the drug has a safe profile with the most common side effects related to gastrointestinal tract complications, photosensitivity and liver

enzyme disturbances. The pooled analysis of the results of the above mentioned studies showed a statistically significant 48% decrease of all-cause mortality (p=0.01) and a statistically significant 68% decrease of IPF-related mortality (p=0.006) for the treated patients in comparison with the placebo arm of the study[5-7].

In October 15th, 2014 FDA authorized the use of another agent: **nintedanib**, for IPF treatment independently of the disease severity status. Nintedanib is a triple tyrosine kinase inhibitor. Approval was based on the results of two phase III trials (**IMPULSIS-1, IMPULSIS-2**)[8], the first showing that the adjusted annual rate of change in FVC was -114.7ml with nintedanib versus -239.9 ml with placebo (difference, 125.3 ml; 95 %CI, 77.7 to 172.8; p<0.001) and the second showing that the adjusted annual rate of change in FVC was -113.6 ml with nintedanib versus -207.3ml with placebo (difference, 93.7ml; 95% CI, 44.8 to 142.7; p<0.001). In IMPULSIS -2 only there was a significant benefit with nintedanib versus placebo in the time to the first exacerbation (hazard ratio, 0.38; 95% CI, 0.19 to 0.77; p=0.005).

Under the light of the above mentioned data and scientific evidence, the review of the therapeutic protocol for IPF in Greece is considered mandatory as follows:

- IPF patients with **mild and moderate disease** (FVC ≥50% pred and DL_{CO} ≥35% pred) should initiate treatment with pirfenidone unless contraindicated. The application of the therapeutic treatment should be undertaken by a pulmonary medicine physician specialized in the management of IPF patients and demands the systematic follow-up of the patients for issues of drug tolerance and effectiveness. Patients should be advised to avoid sun exposure and the drug should not be administered to patients already taking fluvoxamine as well to patients with significant hepatic and renal function disturbances.
- Patients should be informed about the possibility of having access to early treatment access with nintedanib before its awaited EMA approval, through the application of a specific program.

It is furthermore **recommended** that:

- IPF **co-morbidities** such as gastro-eosophageal reflux, obstructive sleep apnea syndrome, depression, cardiovascular disease, neoplastic disease, should be properly diagnosed and adequately treated
- Patients with chronic respiratory failure should receive long term oxygen therapy as indicated
- Pulmonary rehabilitation should be applied as indicated
- IPF patients should systematically undergo prophylactic vaccination against *influenza* virus and pneumococcal disease
- IPF patients should be evaluated for lung transplantation and prescribed in lung transplant lists as indicated
- IPF patients should be informed about the possibility of participating in clinical trials for new therapeutic options (new drugs under investigation, stem cell therapy)

It is of major importance to note that patients with IPF should be managed and followed-up by a specialized team of physicians through the **multidisciplinary approach in referral centers**, just like it is the case for every rare disease like IPF is. This team should include an experienced specialized pulmonary medicine doctor as well as a specialized thoracic radiologist and pathologist, in order to diminish as far as possible the possibility of wrong diagnosis, harmful treatments and inappropriate economic waste[9].

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