Treatment options for IPF: ever changing?

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive lung disease, which is usually fatal with a median survival of only 2 to 5 years following diagnosis. There is a clear unmet need for improved therapy. An optimal drug or combination of drugs should be able to stabilize the disease permanently. Some changes occurred in our treatment approaches. In 2002, the ATS/ERS IPF-statement recommended anti-inflammatory therapy (corticosteroids in combination with azathioprine or cyclophosphamide) for those patients who wished to be treated after appropriate discussion of risks and benefit. In 2005, the IFIGENIA study showed that the addition of high dose N-acetylcysteine (NAC), acting as antioxidant, to prednisone/azathioprine was associated with a reduction in the loss of vital capacity and TLCO at 12 months. This triple therapy was then considered by some institutions as the standard therapy until 2011, when a new era in the management of IPF emerged. Pirfenidone, a drug with anti-fibrotic and anti-inflammatory properties, was approved for the treatment of early and moderate IPF in the European Union as first drug for this indication. The approval was based on the results of 4 randomized, placebo-controlled clinical trials including more than 1.100 patients. Pirfenidone slowed the decline in lung function and reduced the risk of disease progression. Side effects include gastrointestinal discomfort, skin reactions and photosensitivity. Pirfenidone can now be considered as the first line therapy for the given indication in countries where the drug is available.

Following this good news about pirfenidone, in October 2011 the National Heart, Lung, and Blood Institute (NHLBI) announced an alarming press release, that the prednisone/azathioprine/NAC (triple therapy) arm of the PANTHER study had been stopped for safety concerns after the enrolment of 238 of a planned 390 participants. Compared to placebo, patients assigned to triple therapy had greater mortality (11% versus 1%), more hospitalizations (29 percent versus 8 percent), and more serious adverse events (31% versus 9%), and also had no difference in lung function test changes. What does this imply for patients and doctors treating IPF patients? For the moment it seems to be wise to avoid starting new IPF patients with the triple therapy. Patients on current triple therapy, who tolerate this well, with no evidence of progression of IPF, may continue triple therapy. Patients on triple therapy who experienced complications such as infections in the past, may decide to stop this therapy. Importantly, this safety alert applies only to patients with IPF and not to patients taking the triple therapy for other interstitial lung diseases. It is also evident that NAC given as monotherapy may still be an option for IPF patients, since no concerns have emerged for this arm of the PANTHER trial.

With every newly diagnosed IPF patient, the individual treatment options should be discussed, considering their potential benefits and side effects. Most patients will likely prefer pirfenidone as a first line therapy. Those who do not tolerate pirfenidone or are afraid of the specific side effect (photosensitivity) may choose NAC monotherapy. Patients who are progressive under pirfenidone can be switched to NAC and vice versa. One of the best options for patients is still the participation in a clinical trial. Whether pirfenidone should primarily be combined with NAC is under debate. Only a randomized controlled trial can show whether there is an additive effect when combining both compounds. In the future, other drugs may become available, such as the triple kinase inhibitor BIBF 1120 or the anti-CCL-2 monoclonal antibody CNTO 888. Both are currently being tested in clinical trials.

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