Combination Therapies Targeting Multiple Pathways in idiopathic pulmonary fibrosis (IPF)

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Key words: idiopathic pulmonary fibrosis (IPF), pirfenidone, N-acetylcysteine

(Intern Med 52: 2481-2482, 2013)

(DOI: 10.2169/internalmedicine.52.0847)

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and devastating interstitial lung disease, with a median survival from diagnosis of 3-4 years and a 5-year survival below 30% (1). The search for new therapies to treat IPF has intensified since the start of this century, as demonstrated by the increased number of registered clinical trials. However, recent clinical trials of several compounds targeting only a few or single genes, such as interferon γ , endothelin receptor antagonists (bosentan and ambrisentan) and soluble TNF- α receptor antagonists (etanercept), have not resulted in any breakthroughs (1, 2). Therefore, international guidelines for the treatment of IPF state that successful IPF therapy requires a combination of therapeutic modalities targeting multiple pathways involved in fibroproliferation (1). The results of a paper by Sakamoto provide an important suggestion regarding the combined effects of pirfenidone and N-acetylcysteine (NAC) for advanced stage IPF (3).

Pirfenidone plays a multifaceted role, exhibiting antifibrotic, anti-inflammatory and antioxidant effects (1). It is an anti-inflammatory and antioxidant agent that inhibits transforming growth factor- β (TGF- β) *in vitro*. Pirfenidone also acts as an antifibrotic by directly altering the expression, synthesis and possibly accumulation of collagen and inhibiting the recruitment, proliferation and possibly expression of extracellular matrix-producing cells. A recent Cochrane review encompassing four trials involving 1,155 patients compared pirfenidone with placebos (4-7). Three trials involving 1,046 patients provided data for progression-free survival: pirfenidone significantly reduced the risk of disease progression by 30% (HR: 0.70, 95% CI: 0.56 to 0.88, $p=0.002$). Data regarding the effects of pirfenidone on the pulmonary function were assessed in only two studies analyzing 314 patients. In those studies, both the forced vital capacity and vital capacity were significantly improved by pirfenidone treatment (mean difference: 0.08 L, 95% CI: 0.03 to 0.13,

$p=0.0006$). Based on these favorable data, pirfenidone has become the first licensed antifibrotic drug for use in the treatment of IPF in Japan, Europe and Asia. However, the efficacy of pirfenidone in advanced-stage IPF patients remains unclear because the randomized controlled trials (RCTs) conducted to date have included patients in the mild to moderate stage of disease.

NAC, a precursor of the antioxidant glutathione, acts as a scavenger of oxygen free radicals. NAC also directly alters the structure of TGF- β , thus attenuating its profibrotic properties (1). NAC is viewed to be a potentially effective therapeutic compound for the treatment of IPF based on the hope that replenishing glutathione stores will restore the natural oxidant/antioxidant balance and prevent the oxidative injury that precedes fibroproliferation. In the IFIGENIA trial, the addition of oral NAC to corticosteroids and azathioprine was associated with a significantly smaller decline in the pulmonary function. A previous study randomized 30 patients to receive either aerosolized NAC or a placebo for 12 months and documented significant improvement in the extent of ground-glass opacity on computed tomography and reduction in the KL-6 levels. Although the recent randomized trial of aerosolized NAC conducted by Homma et al. did not achieve the primary end point in all subjects, the post hoc analysis showed significantly lower 48-week declines in forced vital capacity (FVC) (a difference of 120-170 mL) in a subset of patients with a mean baseline VC of almost 80% and a DLco of almost 43% of the predicted value (8).

The subjects in Sakamoto's study were characterized by a poor prognosis, including having advanced-stage disease (stage of severity: III & IV according to the Japanese Respiratory Society criteria) and exhibiting disease progression of more than a 10% relative decline in FVC during the preceding six months (3). Pirfenidone treatment stabilized the declines in FVC in eight of 18 patients (44%). In addition, seven of 10 patients receiving combined pirfenidone with

NAC demonstrated disease stabilization and exhibited a better median survival than the eight non-NAC patients (557+/-66 days vs. 196+/-57 days, $p=0.03$). Although this was a retrospective study with a small number of patients, the favorable results prompted us to conduct a well-designed RCT to elucidate the efficacy of combined therapy of pirfenidone and NAC.

It is interesting to note that several recent compounds targeting single genes have failed to meet the primary end point; however, pirfenidone and NAC, which are less broad but still target and affect numerous genes, have been reported to be efficacious for IPF. In addition, this study suggests that multiple-agent therapy that targets the injurious components of disease pathogenesis may have enhanced efficacy for the advanced and progressive stage of IPF. Similar to the progress achieved in the field of advanced lung cancer with multiple-agent therapy including anticancer drugs, we believe that an effective therapeutic strategy for treating advanced IPF will be developed in the near future. Researchers must continue to do their utmost to elucidate the efficacy of possible combination therapies and evaluate novel drugs for this attritional disease.

The authors state that they have no Conflict of Interest (COI).

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