

Another Weapon in the Battle against Idiopathic Pulmonary Fibrosis?

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing disease of the lung without a clear etiology. A number of therapies have been tested for this devastating condition, yet none has demonstrated efficacy in modifying respiratory-specific or all-cause mortality in IPF (1). There are currently only two Food and Drug Administration–approved drugs for the treatment of IPF in the United States: pirfenidone (Esbriet) and nintedanib (BIBF 11200; Ofev). Pirfenidone is a pyridone derivative that exhibits antifibrotic and antiinflammatory effects. Its antifibrotic mechanism is thought to involve downregulation of the production and activity of transforming growth factor- β (TGF- β), a central signaling pathway in organ fibrosis. Nintedanib is a multi-tyrosine kinase inhibitor that was originally used in cancer therapy as an antivascular agent. Its antifibrotic activity is believed to involve interruption of several key growth factor signaling pathways that are important in pulmonary fibrosis, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and fibroblast growth factors (FGFs). Clinical trials have demonstrated the efficacy of both pirfenidone and nintedanib in slowing the decline in forced vital capacity that is characteristic of IPF progression (2–5). Although the approval of these two agents ushered in a new era in IPF treatment, therapeutic options remain limited for patients living with this disease.

In this issue of the *Journal*, Koyama and colleagues (pp. 478–487) describe the first head-to-head comparison of a new multi-tyrosine kinase inhibitor, TAS-115, and nintedanib in cell-based assays and bleomycin-induced fibrosis in mice (6). TAS-115 was first developed by Taiho Pharmaceutical Co. as a highly specific, small-molecule inhibitor of VEGF receptor 2 (VEGFR2) and hepatocyte growth factor receptor (HGFR, or c-MET) for use as an antitumor therapeutic (7). HGF signals through c-MET to upregulate expression of proangiogenic VEGF. Blocking both pathways by suppressing receptor tyrosine kinase phosphorylation with TAS-115 was shown to effectively decrease tumor vascularization and load with minimal toxicity and off-target effects (8). Further work demonstrated that TAS-115 also inhibits signaling through colony-stimulating factor receptor on macrophages (M-CSFR, or c-FMS) as well as PDGF receptor α (PDGFR α) (9, 10). Unlike nintedanib, TAS-115 appears to spare FGF receptors (FGFRs), which may be beneficial as some FGFs are antifibrotic (11). Given that PDGFs play a key role in promoting fibrosis (12) and that macrophages may also contribute to the disease via elaboration of the profibrotic chemokine CCL-2 (13), the authors elected to focus on PDGFRs and c-FMS in this study.

In both the human lung fibroblast cell line MRC-5 and primary mouse lung fibroblasts, TAS-115 inhibited PDGFR phosphorylation in response to PDGF-BB, as well as downstream responses such as cell proliferation and migration. Using mouse bone marrow–derived macrophages, the authors further showed that c-FMS phosphorylation was suppressed by TAS-115, as was production of CCL-2. Daily gavage of bleomycin-treated mice with TAS-115 reduced collagen deposition and the fibrotic disease index in the lung, with TAS-115 as effective as nintedanib at half the dose. Notably, both

TAS-115 and nintedanib at 300 nM had no effect on the expression levels of α -smooth muscle actin and collagen 1 α 1, both of which are markers of fibrosis, in MRC-5 cells stimulated with TGF- β . Other investigators have shown that a reduction in collagen secretion and assembly into fibrils requires at least 1 μ M nintedanib (14, 15). TAS-115 treatment also attenuated lymphocyte numbers as well as levels of proinflammatory (IL-6 and TNF- α) and profibrotic (TGF- β) markers in the BAL fluid at Days 14 and 21. Because TAS-115 did not have this effect at Day 7 after bleomycin treatment, the authors convincingly argue that TAS-115 is a modulator of inflammation associated with fibrosis, rather than acute inflammation resulting from bleomycin-induced injury. Overall, TAS-115 outperformed nintedanib at similar doses in most of the assays in this study, making this compound a promising candidate as an intervention for IPF.

Because TAS-115 dosing in this study was started right after bleomycin, it is not yet clear whether and how well the compound would alter established fibrosis. Nevertheless, the preclinical model suggests that TAS-115 may be useful for blunting the inflammation associated with exacerbations in patients with IPF. Given that the responses of mouse cells and cell lines may not always reflect those of human cells, future work with primary lung fibroblasts and monocyte-derived macrophages from control subjects without IPF (and subjects with IPF) would extend the scope of the study. As an example, the authors note that MRC-5 fibroblasts do not express VEGFR2, which prevented them from addressing this receptor as a potential target for TAS-115. Also of considerable interest for further investigation is how TAS-115 affects signaling through c-MET, a receptor to which both pro- and antifibrotic properties have been ascribed.

Although approval for the use of pirfenidone and nintedanib represented a major milestone in the management of IPF, other treatment options are sorely needed. Earlier this year, Taiho began sponsoring a phase II trial (JapicCTI-183898) to test whether TAS-115 is safe and effective in patients with IPF. TAS-115 and nintedanib target similar signaling pathways, but TAS-115 demonstrates more potent pharmacologic inhibition of these pathways than nintedanib. Time will tell if TAS-115 is a worthy addition to the pharmaceutical armamentarium we have so far to fight this currently fatal lung disease. ■

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