National Jewish Health
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JOURNAL CLUB
Article Summary by: Rebecca Keith, MD

ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Disease. N Engl J Med 2019; 381:1718-1727

CLINICAL QUESTION

Can nintedanib, an intracellular inhibitor of tyrosine kinases, slow progression of lung fibrosis across a broad range of fibrosing lung diseases much like it does in idiopathic pulmonary fibrosis (IPF)?

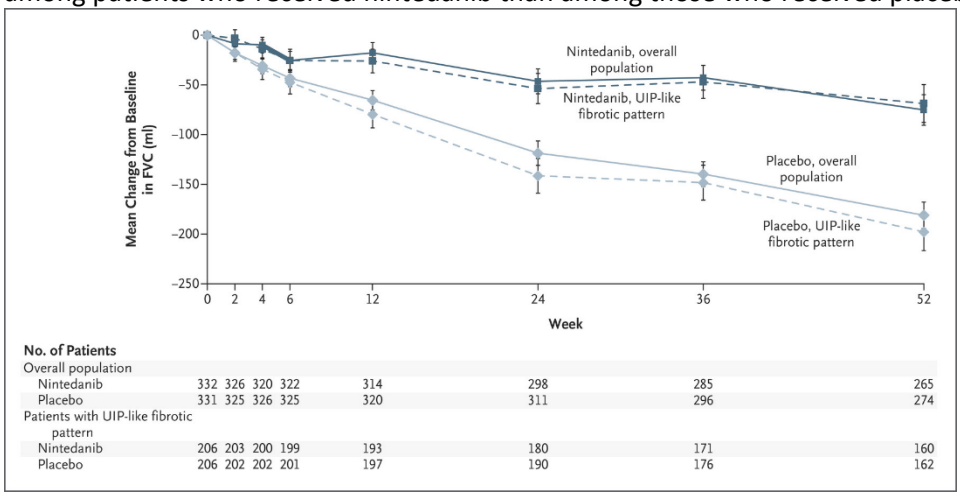
SUMMARY

Many patients with interstital lung disease (ILD) have a progressive fibrosing phenotype characterized by an increasing extent of fibrosis on high-reslolution computed tomography (HRCT), decline in lung function, and worsening of clinical symptoms such as breathlessness. The most well know progressive fibrosing lung disease is IPF. ILD with a progressive phenotype likely has a common pathobiologic mechanism regardless of the cause of the initial ILD and therefore may respond similarly to therapy.

In IPF and systemic sclerosis associated interstitial lung disease, treatment with nintedanib, an intracellular inhibitor of tyrosine kinases, slows progression of pulmonary fibrosis.[1,2] The INBUILD trial was designed to investigate the safety and efficacy of nintedanib in slowing progression in all patients with progressive fibrotic ILD.

INBUILD is a double-blind, placebo-controlled, phase-3 trial conducted in 15 countries. Patients with fibrosing lung disease affecting more than 10% of lung volume on HRCT, who met criteria for progression of ILD in the last 24 months, were randomly assigned to receive nintedanib at 150mg twice daily or placebo. Patients had to have a forced vital capacity (FVC) of at least 45% of the predicted value and a diffusing capacity of the lung for carbon monoxide (DLCO) ranging from 30 to 80% of the predicted value. Patients who were treated with azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, rituximab, cyclophosphamide, or oral glucocorticoids at more than 20mg daily were excluded. The primary end point was the annual rate of decline in FVC as assessed over a 52-week period.

A total of 663 patients were treated. The adjuted rate of decline in FVC was 80.8 ml per year in the nintedanib group and 187.8 ml per year in the placebo group. The annual rate of decline in the FVC was significatinly lower among patients who received nintedanib than among those who received placebo.



No. of Patients								
Overall population								
Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274
Patients with UIP-like fibrotic pattern								
Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162

GROUP OPINION

Patients who received nintedanib had a slower rate of decline than those who received placebo independent of the fibrotic pattern on HRCT. This study supports the idea that progressive fibrosing ILD likely has a similar mechanism regardless of clinical diagnosis. Thus, suggesting that once fibrosis develops it leads to additional fibrosis regardless of the initial insult or pathway that led to the development of fibrosis initially. Finally, the safety and side-effect profile of nintedanib in patients with progressive fibrosing interstitial lung disease is similar to that observed in patients with IPF and systemic sclerosis assoicated interstitial lung disease.

1. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071-82.
2. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis–associated interstitial lung disease. N Engl J Med 2019;380:2518-28

On behalf of the National Jewish Health ILD Program Providers:
Kevin K. Brown, MD
Gregory P. Downey, MD
Evans Fernandez, MD, MS
Stephen Frankel, MD
Tristan J. Huie, MD
Rebecca Keith, MD
Matthew Koslow, MD
Michael P. Mohning, MD
Katherine Rosen, NP
Joshua J. Solomon, MD
Zulma X. Yunt, M.D.