Nintedanib, an Anti-Fibrotic Drug, Preserves Lung Alveolar and Vascular Growth and Prevents Pulmonary Hypertension in an Experimental Model of Hyperoxia-Induced Lung Injury

Kathy Ding, Caroline Smith, Gregory Seedorf, Steven H. Abman,
Pediatric Heart Lung Center, Department of Pediatrics, University of Colorado, Denver Anschutz Medical Center, Aurora, CO 80045

SCHOOL OF MEDICINE
Department of Pediatrics
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Children's Hospital Colorado

BACKGROUND

Bronchopulmonary dysplasia (BPD), the chronic lung disease associated with prematurity, is characterized by decreased alveolar and vascular growth, interstitial fibrosis, and associated comorbidities, including pulmonary hypertension (PH). The pathophysiology of BPD is partly due to hyperoxia-induced postnatal injury, and in addition to impaired distal lung growth, lung fibrosis can contribute to abnormal lung function. Despite marked improvements in the survival of premature newborns, the incidence of BPD has not decreased over the past decades and it remains the most frequent complication associated with extreme prematurity. Therapies directed for the prevention of BPD and BPD-associated PH remain lacking. Recent work has shown that anti-fibrotic agents, including Nintedanib, can preserve lung function in adults with idiopathic pulmonary fibrosis. Whether early Nintedanib treatment can prevent BPD by preserving lung alveolar and vascular growth, improving lung function, and reducing the development of PH is unknown. It is further unclear whether Nintedanib, which is a tyrosine kinase receptor inhibitor, has adverse effects on the developing lung.

OBJECTIVE

To determine if Nintedanib treatment will preserve lung alveolar and vascular growth, improve lung function and prevent PH in a postnatal hyperoxia model of BPD in rats.

METHODS

Newborn rats were exposed to either hyperoxia (90%) or room air (RA) conditions and received daily treatment of Nintedanib or saline (control) by intraperitoneal (IP) injections (1 mg/kg) for 14 days. At day 14, lung mechanics were measured before rats were killed to harvest lung and cardiac tissue. Lung mechanics, including total respiratory resistance and compliance, were measured using a flexiVent system. Lung tissue was then evaluated for radial alveolar counts (RAC), mean linear intercept (MLI), and pulmonary vessel density (PVD). Right ventricular hypertrophy (RVH) was quantified with cardiac weights using Fulton's index (ratio of right ventricle to the left ventricle plus septum).

RESULTS

When compared with RA controls, hyperoxia exposure reduced RAC by 64% ($p<0.01$) and PVD by 65% ($p<0.01$) and increased MLI by 108% ($p<0.01$). and RVH by 118% ($p<0.01$). Hyperoxia increased total respiratory resistance by 94% and reduced lung compliance by 75% ($p<0.01$ for each). Nintedanib administration restored RAC, MLI, RVH, and total respiratory resistance to control values and improved PVD and total lung compliance in the hyperoxia-exposed rats. Nintedanib treatment of control animals did not have adverse effects on lung structure or function at doses used in this study.

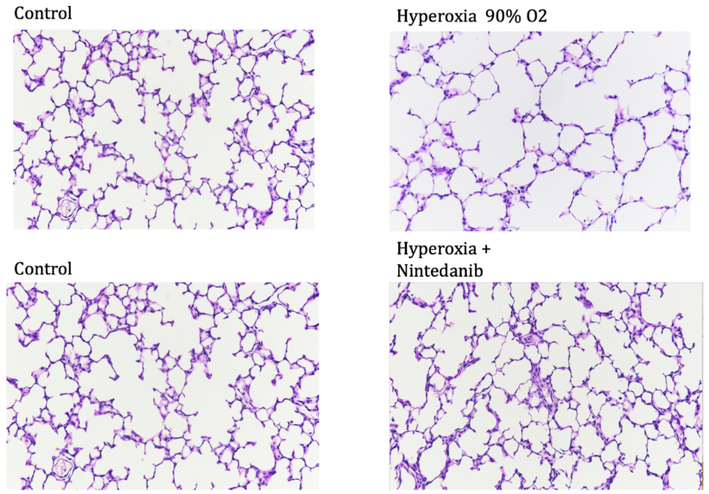
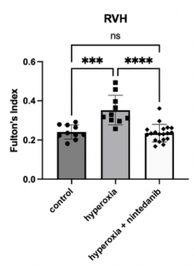
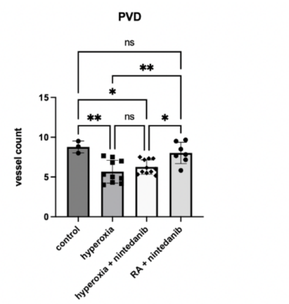


Figure 1. Histological comparison of alveolar structure in controls vs 90% hyperoxia conditions vs hyperoxia conditions and Nintedanib treatment.



Uncorrected Dunn's test		Summary	p-value
control vs. hyperoxia		***	0.001
control vs. hyperoxia + nintedanib		ns	0.7794
hyperoxia vs. hyperoxia + nintedanib		****	<0.0001

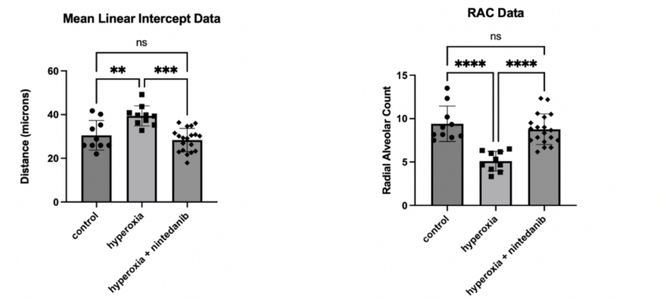
Figure 2. Graphical comparison and statistical significance of right ventricular hypertrophy in controls, hyperoxia conditions, and hyperoxia conditions with Nintedanib treatment.



Uncorrected Dunn's test	Summary	Individual P Value
control vs. hyperoxia	**	0.0026
control vs. hyperoxia + nintedanib	*	0.0154
control vs. RA + nintedanib	ns	0.5039
hyperoxia vs. hyperoxia + nintedanib	ns	0.3579

Figure 3. Graphical comparison and statistical significance of pulmonary vessel density in controls, hyperoxia conditions, and hyperoxia conditions with Nintedanib treatment.

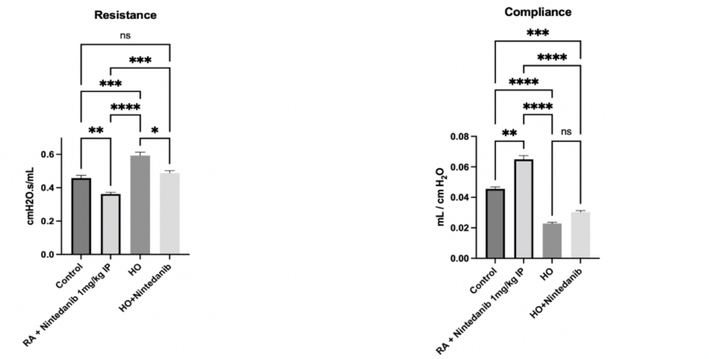
RESULTS



Uncorrected Dunn's test		Summary	p-value
control vs. hyperoxia		**	0.0044
control vs. hyperoxia + nintedanib		ns	0.5434
hyperoxia vs. hyperoxia + nintedanib		***	0.0001

Uncorrected Dunn's test		Summary	p-value
control vs. hyperoxia		****	<0.0001
control vs. hyperoxia + nintedanib		ns	0.5067
hyperoxia vs. hyperoxia + nintedanib		****	<0.0001

Figure 4. Graphical comparison and statistical significance of mean linear intercept and radial alveolar counts for controls, hyperoxia conditions, and hyperoxia with Nintedanib treatment.



Uncorrected Dunn's test		Summary	p-value
Control vs. RA + Nintedanib 1mg/kg IP		**	0.0036
Control vs. HO		***	0.0002
Control vs. HO+Nintedanib		ns	0.1611
RA + Nintedanib 1mg/kg IP vs. HO		****	<0.0001
RA + Nintedanib 1mg/kg IP vs. HO+Nintedanib		***	0.0004
HO vs. HO+Nintedanib		*	0.028

Uncorrected Dunn's test		Summary	p-value
Control vs. RA + Nintedanib 1mg/kg IP		**	0.0016
Control vs. HO		****	<0.0001
Control vs. HO+Nintedanib		***	0.0003
RA + Nintedanib 1mg/kg IP vs. HO		****	<0.0001
RA + Nintedanib 1mg/kg IP vs. HO+Nintedanib		****	<0.0001
HO vs. HO+Nintedanib		ns	0.139

Figure 5. Lung mechanics data gathered from flexiVent system. Comparisons are made for total respiratory resistance and compliance between controls, room air and Nintedanib treatment, hyperoxia conditions, and hyperoxia with Nintedanib treatment.

CONCLUSION

Nintedanib treatment preserved lung alveolar and vascular growth, improved lung function and reduced RVH in the hyperoxia model of BPD in neonatal rats, without apparent adverse effects in controls. We speculate that Nintedanib may provide a novel therapy for the prevention of BPD.