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Title: Effect of nintedanib on silica-induced lung inflammation and fibrosis in mice

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Body: Introduction: One-year treatment with the receptor tyrosine kinase inhibitor nintedanib (BIBF 1120) specific for vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR) was associated with a 68.4% reduction in the rate of decline of forced vital capacity in patients with idiopathic pulmonary fibrosis (IPF) versus placebo, which approached statistical significance. Aim: To further explore its mode of action, nintedanib was tested in a mouse model of silicosis displaying ongoing pulmonary inflammation and fibrosis. Methods: Within 30 days a single intranasal administration of silica caused a robust lung inflammation with a significant increase in macrophages, neutrophils and lymphocytes in the BALF, increased IL-1 beta, CXCL1/KC and TIMP1 production, and increased collagen deposition in the lung. Histologic analysis revealed chronic inflammation with granuloma formation and fibrosis demonstrated by collagen staining. Results: Nintedanib administered by gavage at 30 and 100 mg/Kg/day significantly reduced neutrophil and lymphocyte counts, but had no effect on macrophage counts in the BALF. Furthermore, IL-1 beta, CXCL1/KC, TIMP1, collagen in lung and lung inflammation with granuloma and fibrosis were drastically reduced. Conclusion: Nintedanib effectively reduced silica-induced chronic inflammation and fibrosis in mice. The anti-inflammatory and anti-fibrotic features of nintedanib may impact the progressive course of fibrotic lung diseases like IPF or silicosis.