

PBI-4050, a novel first-in-class anti-inflammatory/fibrotic compound, reduces bleomycin-induced idiopathic pulmonary fibrosis by regulating inflammatory cytokines in bronchoalveolar fluid



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BACKGROUND

The pathobiological mechanisms underlying the development of idiopathic pulmonary fibrosis (IPF) are highly complex. PBI-4050, a novel first-in-class, orally active low molecular weight compound, plays a key role in inflammation/fibrosis regulation by reducing pro-fibrotic cytokines, fibrocyte differentiation, myofibroblast activation and EMT, resulting in improvement of organ function.

The aim of this study was to determine the effect of PBI-4050 on the regulation of bronchoalveolar lavage fluid (BALF) inflammatory cytokines involved in bleomycin-induced IPF.

STUDY DESIGN

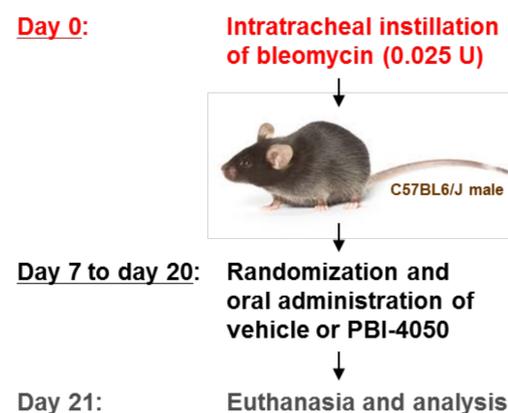


Figure 1: Study design. Mice were randomized according to their bleomycin-induced body weight loss, and treatments with PBI-4050 started on day 7. Only animals that recovered their body weight loss by day 20 were used for data analysis.

A. Effect of oral treatment with PBI-4050 on inflammatory cytokines in BALF

Intratracheal instillation of bleomycin induces a significant increase in CTGF (Figure 2), IL-1 β (Figure 3) and TNF- α (Figure 4) in BALF. Treatment with PBI-4050 reduced the amount of CTGF in BALF close to the level observed in the control group (sham), while IL-1 β and TNF- α levels in BALF were reduced by 20-30% in PBI-4050-treated mice.

B. Effect of PBI-4050 treatment on lung fibrosis

Regulation of these cytokines correlated with the histological observation from HEP and Masson's trichrome staining of the lung tissue. Visual grading of pulmonary fibrosis was determined according to Ashcroft's score (Figure 5). Briefly, the entire fields of each lung section were read by a blinded examiner, and each field was visually graded from 0 to 8. Criteria for grading lung fibrosis were as follows:

- Grade 0=Normal lung
- Grade 1=Minimal fibrous thickening of alveolar or bronchiolar walls
- Grade 3= Moderate thickening of walls without obvious damage to lung architecture
- Grade 5=Increased fibrosis with definitive damage to lung structure and formation of fibrous bands or small fibrous masses
- Grade 7=Severe distortion of structure and large fibrous area
- Grade 8=Total fibrous obliteration of lung fields

RESULTS

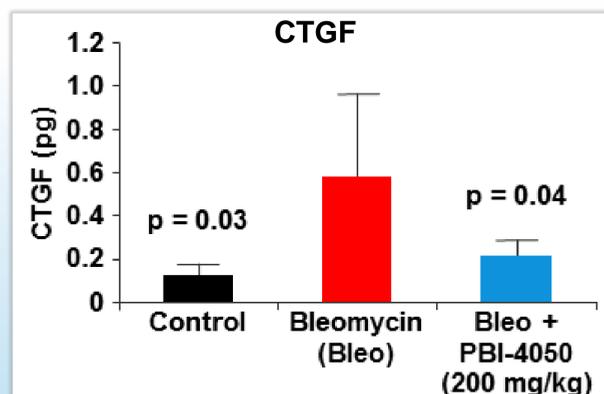


Figure 2: Effect of PBI-4050 on CTGF level in BALF in bleo-induced lung fibrosis.

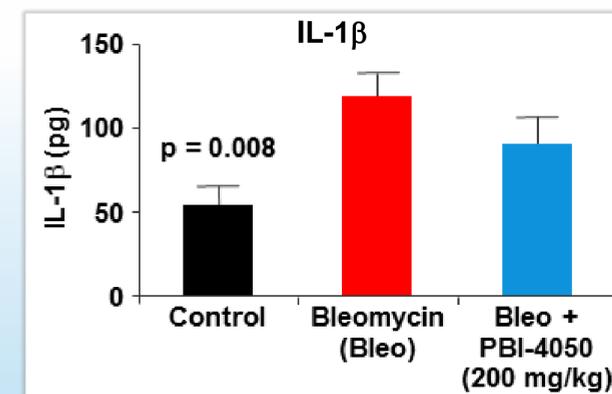


Figure 3: Effect of PBI-4050 on IL-1 β protein level in BALF in bleo-induced lung fibrosis.

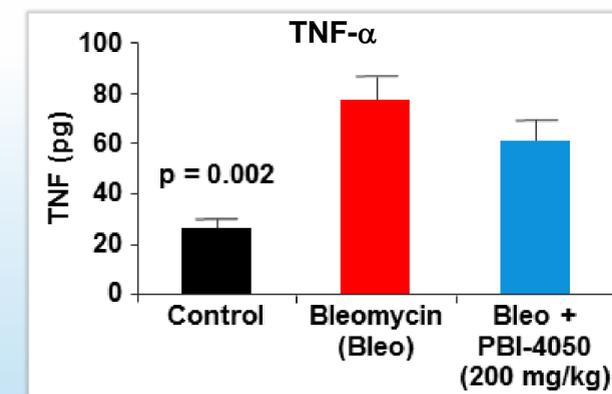


Figure 4: Effect of PBI-4050 on TNF- α protein level in BALF in bleo-induced lung fibrosis.

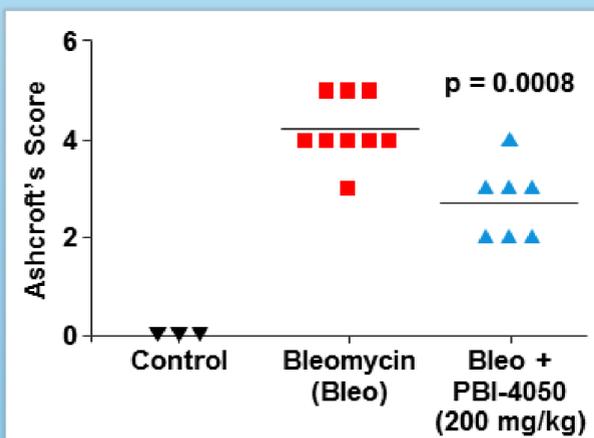


Figure 5: Ashcroft's score (HEP and Masson's Trichrome staining). PBI-4050 induced a significant decrease of lung fibrosis under ANOVA/Dunnett's analysis.

Masson's stain showed that alveolar spaces were widened and filled with collagen fibers (Figure 6), indicating proliferative fibroblastic lesions in bleomycin-induced lung fibrosis that were reduced with oral treatment with PBI-4050 when graded according to Ashcroft's method.

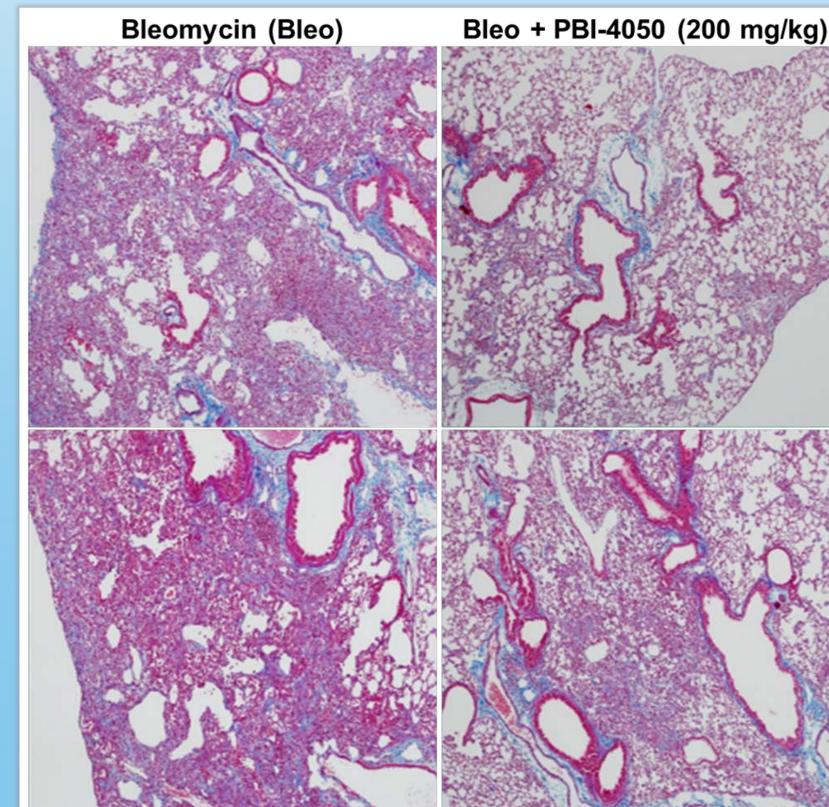


Figure 6: Photomicrographs of lung tissue from mice treated with PBI-4050 showing significant reduction of fibrosis (Masson's Trichrome staining, 40X) by PBI-4050.

CONCLUSION

Our results show that oral treatment with PBI-4050:

- ❖ Reduces the amount of pro-inflammatory/pro-fibrotic cytokines in BALF
- ❖ Reduces histological lesions

PBI-4050 may be an efficacious treatment in IPF by prevention of the progression of lung injury resulting from reduced tissue fibrosis and regulation of key cytokines