PBI-4050, a novel first-in-class anti-fibrotic compound, reduces lung fibrosis in the bleomycin-induced lung fibrosis model: a comparative study with pirfenidone

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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 is to compare the anti-fibrotic activity of PBI-4050, pirfenidone and combination of both compounds in the bleomycin-induced lung fibrosis model.

STUDY DESIGN

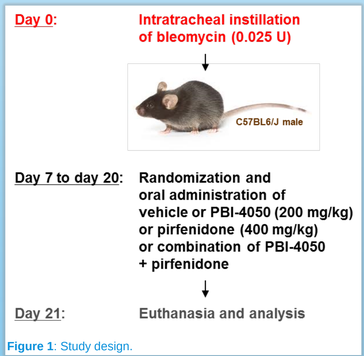

Figure 1: Study design.

Mice were randomized according to their bleomycin-induced body weight loss, and treatments with PBI-4050 and pirfenidone or combination of both compounds started on day 7. Only animals that recovered their body weight loss by day 20 were used for data analysis.

RESULTS

A. Effect of treatment regimen on inflammatory/pro-fibrotic cytokines mRNA expression in lung

Bleomycin induced a significant increase in mRNA expression of all key mediators in the lung. PBI-4050 and combination therapy significantly decreased TGF-β1 (Figure 2), CTGF (Figure 3), IL-23p19 (Figure 4) and IL-6 (Figure 5) expression in lung, while pirfenidone had no effect on CTGF.

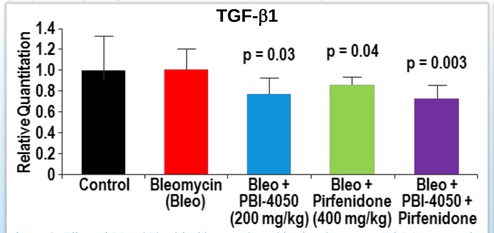

Figure 2: Effect of PBI-4050, pirfenidone and combination therapy on TGF-β1 expression in bleomycin-induced lung fibrosis.

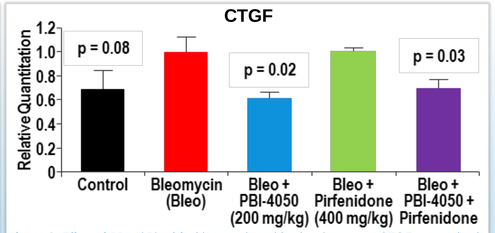

Figure 3: Effect of PBI-4050, pirfenidone and combination therapy on CTGF expression in bleomycin-induced lung fibrosis.

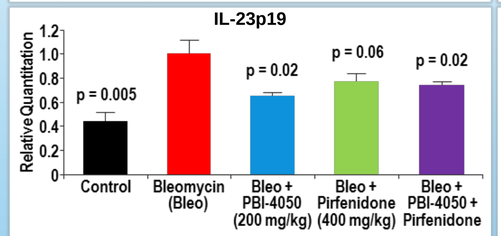

Figure 4: Effect of PBI-4050, pirfenidone and combination therapy on IL-23p19 expression in bleomycin-induced lung fibrosis.

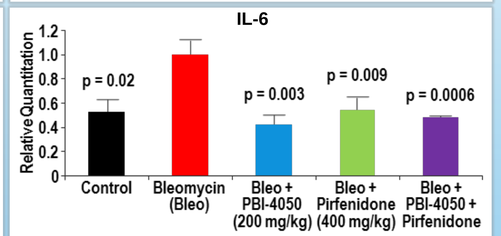

Figure 5: Effect of PBI-4050, pirfenidone and combination therapy on IL-6 expression in bleomycin-induced lung fibrosis.

B. Effect of treatment regimen on fibrotic markers mRNA expression in lung

IPF is characterized by exaggerated fibroblast proliferation and accumulation of collagens and fibronectin. All treatments induced a significant reduction of collagen I (Figure 6) and fibronectin 1 (Figure 7) expression to the control level (no bleomycin).

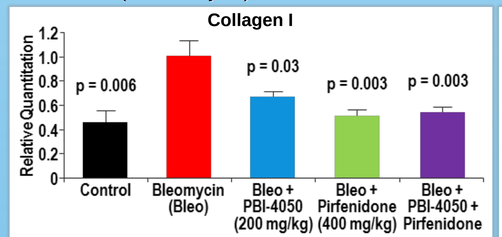

Figure 6: Effect of PBI-4050, pirfenidone and combination therapy on collagen I expression in bleomycin-induced lung fibrosis.

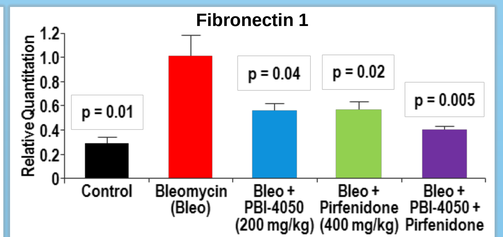

Figure 7: Effect of PBI-4050, pirfenidone and combination therapy on fibronectin 1 expression in bleomycin-induced lung fibrosis.

C. Effect of treatment regimen on remodeling markers mRNA expression in lung

Bleomycin induced a significant increase in mRNA expression of SPARC and MMP-2. PBI-4050 and combination therapy reduced SPARC expression while pirfenidone had no effect (Figure 8). MMP-2 mRNA expression was significantly reduced in the combination therapy (Figure 9).

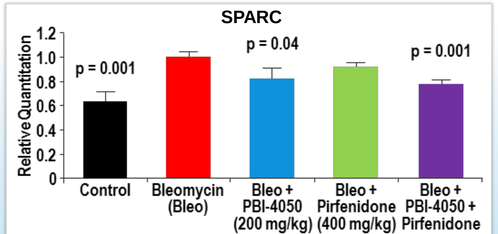

Figure 8: Effect of PBI-4050, pirfenidone and combination therapy on SPARC expression in bleomycin-induced lung fibrosis.

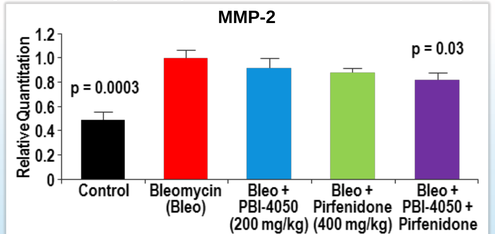

Figure 9: Effect of PBI-4050, pirfenidone and combination therapy on MMP-2 expression in bleomycin-induced lung fibrosis.

D. Effect of treatment regimen on lung fibrosis

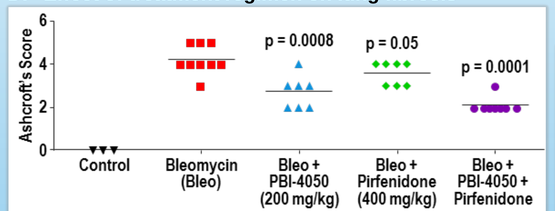

Figure 10: Ashcroft's score (HEP and Masson's Trichrome staining). PBI-4050 and combination therapy were both significantly reduced compared to bleomycin under ANOVA/Dunnett's analysis.

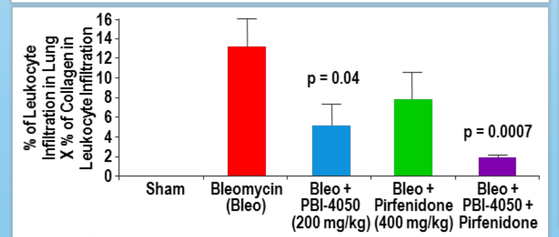

Figure 11: Effect of PBI-4050, pirfenidone and combination therapy on lung collagen in leukocyte infiltrates quantified by histomorphometric analysis.

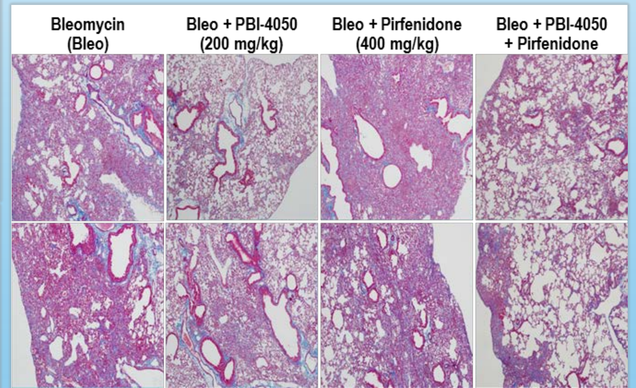

Figure 12: Photomicrographs of lung tissue from mice treated with PBI-4050 showing significant reduction of fibrosis (Masson's Trichrome staining, 40X) by PBI-4050.

CONCLUSION

Our results show that PBI-4050 and combination of PBI-4050 and pirfenidone:

- Reduce inflammatory/profibrotic cytokines (TGF-β1, CTGF, IL-23p19 and IL-6) mRNA expression
- Reduce fibrotic markers (collagen I and fibronectin 1) mRNA expression
- Reduce remodeling markers (SPARC and MMP-2) mRNA expression
- Reduce histological lesions

PBI-4050 may be an efficacious treatment in IPF.

The combination therapy with pirfenidone provides superior outcomes.