Evaluation of Brilaroxazine (RP5063) in a Bleomycin-Induced Rodent Model of Idiopathic Pulmonary Fibrosis

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and debilitating lung disease with a global prevalence of ~ 3 million, 2-5 years median survival time, and 50,000 annual U.S. deaths. It involves chronic inflammation and progressive alveolar fibrosis, leading to destroyed architecture, reduced capacity, impaired oxygenation, and declined function.1-5 Sclerostitis (S-HT) plays a key role, via S-HT2B/3 receptors, in IPF’s pathology involving a vasoactive effect on pulmonary arterioles and lung neovascularization.6-9 Brilaroxazine displays a high affinity for D2/3/4 and 5-HT2A/2B/7 receptors and moderate efficacy for the serotonin transporter.7-10 Its actions on vascular fibrosis (S-HT, receptor), proliferation (S-HT2B receptor), inflammation (S-HT2C receptor), and pro-inflammatory cytokines have created interest in IPF.11-13

OBJECTIVE

This study evaluated whether Brilaroxazine (15 mg twice daily) started on Day 2 or Day 10, displays efficacy in a bleomycin (BLM) induced rat model of IPF.

METHODS

The study design (Figure 1) involved:

• Day 2: Four groups of Sprague Dawley rats received BLM induction and one placebo (Sham) on Day 2.

• Day 2: One group started on bronchial artery (HT) on Day 2. Two groups continued on vehicle (Veh) on Day 2.

• Day 10: One group (n=10) started on bronchial artery induction (HT) and one was continued on BLM on Day 10. All groups continued until Day 20.

• Day 2: Investigators collected hemodynamic parameters (systemic arterial blood pressure, heart rate, and oxygen saturation) and blood samples. They sacrificed the animals, then collected bronchoalveolar lavage fluid (BALF), lung, trachea, and heart tissues.

RESULTS

Survival curves from Day 1-10 (A) and Day 11-21 (B), and body weights (C) of Sham, BLM-induced, and treatment group animals were obtained. Brilaroxazine, via its actions on fibrosis and inflammation involving the pulmonary vasculature and pulmonary vascular endothelial and smooth muscle cell effects.

DISCUSSION

This study was the first preclinical evaluation of Brilaroxazine’s effects on IPF and was consistent with standard models.14-19 Brilaroxazine impacted mortality and functionality, plus inflammation and fibrosis. It positively altered survival, body weight, lung lesions, Brilaroxazine cytokine production, hydroxyproline content, inflammatory, and cardiorespiratory capacity. RT effects were significant across a broader parameter array. Hypothesis may be limited due to BLM induction methods (i.e., mortality) and Day 21 sacrifice. Improvements might be related to the multiple effects via S-HT2B, which other 5-HT2B receptor antagonists have observed. The decrease in BLM-induced up-regulated hydroxyl radical content supports Brilaroxazine’s antioxidant role inhibition of multiple cytokines and modulation of fibrosis.8,16 This study highlighted Brilaroxazine’s potential to modulate inflammation and fibrosis using cytokine levels.17-19 Further studies in preclinical and clinical models are needed to determine its anti-fibrotic potential.

CONCLUSION

Brilaroxazine in relevant in its ability to modulate pulmonary inflammation and eosinophils via 5-HT2B, significantly improved key endpoints and biomarkers in this BLM-induced IPF.

REFERENCES


DISCLOSURES & ACKNOWLEDGEMENTS

Conflicts of Interest: Laxminarayan Bhat and Seema R Bhat are employees of Reviva Pharmaceutical Holdings, Inc.

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