Prophylactic or therapeutic AQX-1125, a small molecule SHIP1 activator, inhibits bleomycin-induced pulmonary fibrosis in mice

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Rationale: SH2-containing inositol-5'-phosphatase 1 (SHIP1) dephosphorylates PI(3,4,5)P3 to yield PI(3,4)P2. SHIP1-deficient mice exhibit progressive pulmonary inflammation and develop evidence of pulmonary fibrosis. Pharmacological activation of SHIP1 has emerged as a potential novel approach to regulate pulmonary inflammation, with pre-clinical and clinical studies showing an anti-inflammatory effect of AQX-1125, a small molecule SHIP1 activator. Here we tested the effect of prophylactic or therapeutic AQX-1125 administration in a murine model of bleomycin-induced pulmonary inflammation and fibrosis.

Methods: The efficacy of AQX-1125, administered by oral gavage (3, 10 or 30 mg/kg), was assessed in bleomycin-induced lung fibrosis in male CD-1 mice. In the prophylactic investigation, bleomycin (0.1 IU/mouse) was administered two h after the third dose of AQX-1125. For therapeutic investigation, AQX-1125 was administered starting on Day 13 after bleomycin administration (0.05 IU/mouse). AQX-1125 administration continued once per day throughout the remainder of the studies. Twenty-one-days (prophylactic investigation), or 28-days (therapeutic investigation) after bleomycin administration, mice were sacrificed and bronchoalveolar lavage (BAL) cellular content, lung edema, myeloperoxidase, TGF-β, histopathology, collagen deposition and mortality determinations were made.

Results: In the 21-day prophylactic model, AQX-1125 significantly (p<0.05) suppressed bleomycin-induced collagen deposition, inflammation and mortality. Moreover, therapeutically administered AQX-1125 also dose-dependently reduced the mortality to bleomycin over the duration of the study. In addition, therapeutic AQX-1125 (10 or 30 mg/kg) significantly (p<0.05) attenuated the bleomycin-induced collagen deposition in the airways by 43% and 82% respectively; which correlated with significantly suppressed leukocyte infiltration of the airways, lung tissue edema, myeloperoxidase activity, TGF-β concentration and the histopathology score (p<0.05).

Conclusions: Therapeutic or prophylactic SHIP1 activation with AQX-1125 inhibits mortality, leukocyte accumulation, edema, inflammatory mediator and collagen content of the airways in a murine model of bleomycin-induced fibrosis. Thus, AQX-1125 has the potential to be developed as a treatment for fibrotic disease.