ATYR1923 Modulates the Inflammatory Response in Experimental Models of Interstitial Lung Disease

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Abstract

Potent antifibrotic activity has been discovered for a novel inhibitor of the cytokine-kinase 6 (CK6) pathway. ATYR1923 is a human IgG1 Fc fusion protein that engages the hepatocyte growth factor receptor (HGFR) to inhibit CK6 signaling. This activity is associated with suppression of fibroblast proliferation, extracellular matrix production, and myofibroblast differentiation. This study shows that ATYR1923 reduces inflammation in animal models.

Introduction

Resolvine Family of Molecules

Successfully treated animal models of acute and chronic lung injury with ATYR1923, a human IgG1 Fc fusion protein.

Weeks Dosing with ATYR1923 Ameliorates Fibrosis in Mouse Models of Bleomycin-induced Lung Injury

Experiments were designed to assess the impact of ATYR1923 on lung fibrosis and inflammation in: *C. elegans* and 5 species of mice, all with different respiratory conditions.

Early Intervention With ATYR1923 Improves Respiratory Function in a Rat Bleomycin Model

Methods: Four Experimental Models of ILD

**5. rectangles**

- Repeated challenges with 5. rectangles react in the most common mode of experimental chronic respiratory hypersensitivity (CRH).
- It features a control form of CRH, which is caused by exposure to sensitized 5. rectangles.
- Test articles were dosed until study termination.

**P. across**

- P. across has been implicated as the pathological agent for sarcoïdosis.
- Repetitive P. across is pathogenic for granulomatous inflammation.
- Test articles were dosed until study termination.

**SKG**

- SKG mice are genetically prone to develop autoimmune arthritis.
- Establishing cytokine-kinase, SKG mice develop a disease resembling rheumatoid arthritis associated interstitial lung disease (AA-ILD) with persistence of an autoantibody to type II collagen.
- Test articles were dosed until study termination.

**cGVHD**

- Mice after graft host disease (cGVHD) inducer symptoms resembling the disease affecting immune-reconstituted mice under transfusion.
- 5.6 monocytes (PVV-10) strain compatibility antigen mismatched transplant model used to induce GVHD.
- Test articles were dosed until study termination.

Results: ATYR1923 Modulates Histopathological Endpoints in Models of SSc and CHP

- Lung tissue was analyzed from mouse models to assess cytokine expression.
- Data were quantified using the HSCORE image analysis platform.

- *Hypersensitivity pneumonitis (HP)*: Test文章 were dosed until study termination.

- *Chronic obstructive pulmonary disease (COPD)*: Test articles were dosed until study termination.

Summary

- ATYR1923 has antifibrotic activity in a murine model of bleomycin-induced chronic GVHD.
- *Antibody activity as determined by in-vivo assays and histopathology samples compared to controls.*
- *Collagen remodeling and hydroxyproline content in lungs of ATYR1923 treated animals were also reduced significantly.*
- *No difference in lung cytokine levels detected at termination (day 30).* This likely is due to resolution of the early cytokine inflammation stage when several cytokines release and baseline, and hence no effect of ATYR1923’s antifibrotic activity.

- *ATYR1923 treatment led to reduction of several key inflammatory protein in lung granuloma forming, highly inflammatory models of ILD (5. rectangles - CHP; P. across - CAVH).*
- *ATYR1923 treatment at 3 mg/kg also lowered terminal BALF area in the 5. rectangles model.*
- *Significant reduction of infiltrating immune cells in a model of RA-ILD (SKG) upon ATYR1923 treatment.*
- *T and B cells, which were implicated in RA-ILD pathogenesis, were significantly lower in lungs of ATYR1923 treated animals.*
- *Low incidence of ILD in the model (~35%) potentially contributed to the lack of significant antifibrotic effects of ATYR1923 when compared to its control group.*

Conclusions

- Provided first evidence that ATYR1923 modulates inflammatory responses following lung injury, which may inhibit subsequent fibrotic processes.

- The robust antifibrotic activity of ATYR1923 across multiple experimental models of ILD can inform selection of additional indications for ATYR1923 therapy.

Stage-dependent anti-inflammatory and antifibrotic effect of ATYR1923 in experimental models of ILD

**SKG**

- Reduced increased infiltrates
- Reduced fibrosis

**cGVHD**

- Reduced profibrotic protein
- Reduced collagen content

Clinical Program

- A Phase 1 study in healthy volunteers was successfully completed in 2018.
- A clinical Phase 1b trial with ATYR1923 for treatment of pulmonary sarcoidosis was initiated in December 2018 (NCT03672142).
- Randomized, double-blind, placebo-controlled, study will evaluate the safety, tolerability, immunogenicity, pharmacokinetics (PK), and preliminary efficacy of multiple ascending doses of 10 ATYR1923 in patients with pulmonary sarcoidosis undergoing a protocol-guided oral corticosteroid (OCS) tapering regimen.

References