A novel, highly specific TGFβ1 inhibiting antibody demonstrates antifibrotic activity without cardiotoxicity


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ABSTRACT

Objective: Transforming growth factor (TGF) β has been shown to drive fibrosis in multiple tissue types and is a potential target for the treatment of fibrotic disease. Despite the promise preclinical data with TGFβ inhibitors, no TGFβ1-selective inhibitors are currently in clinical development. We recently described a novel antibody, SR-AB1, a human monoclonal antibody that specifically targets latent TGFβ1, and a combination of a small molecule TGFβ signaling inhibitor, SR-600, and SR-AB1 that potently inhibited TGFβ1 signaling in vitro and in vivo.

Methods: We conducted a 4-week toxicology study with the ALK5 inhibitor (small molecule) dosed daily for 5 days in rats. We used OCT studies of liver fibrosis and histological analysis of cardiac and kidney tissues to evaluate fibrosis and cardiotoxicity.

Results: No cardiotoxicity was observed. Histological analysis of cardiac and renal tissues showed no fibrosis, and OCT studies demonstrated no change in fibrosis area.

Conclusions: This study supports the development of SR-AB1 as a specific and selective inhibitor of TGFβ1, providing a tool to evaluate efficacy in a range of fibrotic diseases.

Keywords: TGFβ1, fibrosis, non-cardiac toxicity, OCT, antibody

Toxicology Study

- ALK5 inhibitor (small molecule) dosed daily for 5 days
- OCT in liver, heart, and kidneys
- Histological analysis of cardiac and kidney tissues

Background

- Three TGFβ isoforms: TGFβ1, TGFβ2, TGFβ3
- TGFβ1 is the predominant isoform in fibrotic tissues
- TGFβ1 is a multifunctional cytokine involved in multiple biological processes

Methods

- In a 4 week toxicology study in rats with ALK5 inhibitor
- OCT in liver, heart, and kidneys
- Histological analysis of cardiac and kidney tissues

Results

- No cardiotoxicity observed
- Histological analysis of cardiac and renal tissues showed no fibrosis
- OCT studies demonstrated no change in fibrosis area

Conclusions

- SR-AB1 is a specific and selective inhibitor of TGFβ1
- This study supports the development of SR-AB1 as a potential therapeutic agent for fibrotic diseases

Keywords: TGFβ1, fibrosis, non-cardiac toxicity, OCT, antibody