Background & Objectives

- Mesangial cell (MC) activation by IgA-immune complexes is the initiating intra-renal event in the pathogenesis of IgAN.1
- Subsequent MC-podocyte crosstalk results in proteinuria, the strongest predictor of progression.2
- However, the molecular mechanisms responsible have not been well defined.
- The objective of these studies was to determine the role of the ETA receptor in MC activation and subsequent podocyte in IgAN and other mesangio-proliferative glomerulopathies, using the potent and selective ETA antagonist atrasentan.

Methods and Materials

Primary human renal mesangial cells (HRMCs) in culture (64 passages), were stimulated with ET-1 (4 nM) for up to 72 hours ± atrasentan and proliferation (Brdu) and cytokine production (ELISA) were measured. Global transcriptional responses were assessed at 24 h by RNASeq.

IgA-complexes were isolated from the serum of either IgAN patients or age and sex matched healthy controls using jacalin-agarose affinity chromatography2 and applied to HRMCs in culture for 72 hours ± atrasentan; proliferation was analyzed by BrdU incorporation. Global transcriptional responses were assessed at 24 h by RNASeq.

Primary human renal mesangial cells

Results (continued)

D Atrasentan reduced proteinuria and kidney weight in anti-Thy1.1 induced mesangio-proliferative GN

E Atrasentan attenuated glomerular and tubulointerstitial injury histologically in anti-Thy1.1 induced mesangio-proliferative GN

F Atrasentan was recently reported to rapidly reduce albuminuria and downregulate intra-renal pro-inflammatory and pro-fibrotic transcriptional networks in the gdf11 mouse model of spontaneous IgAN - WCN21-0358.

Conclusion

- These studies suggest an important role of the ETA receptor in mesangial cell activation and subsequent proteinuria in IgAN and other models of immune mediated mesangio-proliferative GN.
- These results support the therapeutic potential of atrasentan in IgAN patients, not only via its well characterized effect to reduce proteinuria, but also by potentially reducing mesangial cell activation, a hallmark of IgAN and other mesangio-proliferative glomerulopathies.

- The Phase 3 ALIGN trial is assessing the efficacy, safety and tolerability of atrasentan in IgAN patients at risk of progressive kidney function loss, despite optimized RAS blockade. (ClinicalTrials.gov Identifier: NCT04573478)

References

2. Novak et al., Kidney Int. 67(2): S04-13, 2005

A central role of Endothelin A (ETA) Receptor Activation in Mesangial Cell – Podocyte Crosstalk In IgA Nephropathy and Other Mesangio-Proliferative Glomerulopathies

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