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Selective ET_A Antagonist Atrasentan, Rapidly Reduces Albuminuria and Downregulates Intra-renal Pro-Inflammatory and Pro-Fibrotic Transcriptional Networks in the gddY Mouse Model of Spontaneous IgA Nephropathy

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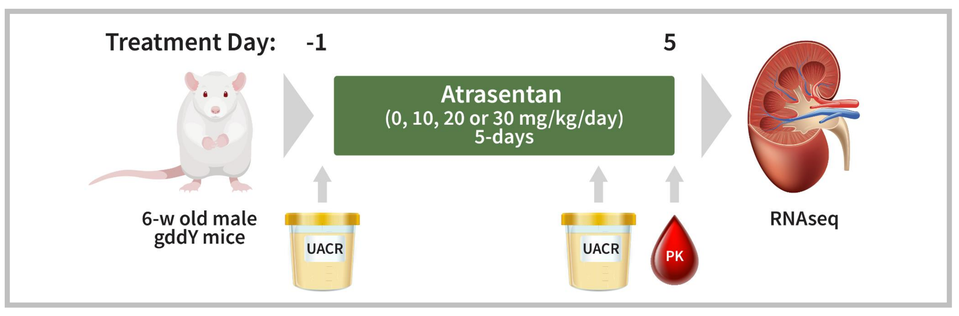
Background

Endothelin pathway activation, which has been observed in kidney biopsies from IgA nephropathy (IgAN) patients, may be an important driver of disease progression by promoting proteinuria along with kidney inflammation and fibrosis via ET_A receptor activation.[1,2,3] Atrasentan is a potent and selective ET_A antagonist which has demonstrated rapid and sustained reductions in proteinuria, preservation of kidney function and improved kidney outcomes in diabetic kidney disease patients.[4] However, the effects of atrasentan have not been previously investigated in IgAN. The **objective** of this study was to evaluate the effect of short-term treatment of varying doses of atrasentan in the gddY mouse model of spontaneous IgAN, with a focus on dynamic changes in the intra-renal transcriptional profile.

The gddY mouse is a spontaneous model of early-onset IgAN characterized by IgA immune complex deposition in the mesangium of the kidney, leading to significant proteinuria, glomerular hypercellularity, mesangioproliferative glomerular lesions, glomerulosclerosis and reduced kidney function, all hallmarks of human IgAN.[5]

Methods



- 6-week-old male gddY mice were administered atrasentan (10, 20 or 30 mg/kg/day, n=3/group or 0 mg/kg/day, n=2/group) in drinking water for 5 days
- Urine albumin to creatinine ratio (UACR) was measured at baseline and on Day 4 of treatment
- On Day 5, a terminal plasma sample was collected for the measurement of atrasentan plasma concentrations and kidney cortex was flash-frozen for RNA-seq which was analyzed by pairwise differential gene expression using edgeR's quasi-likelihood F-test (FDR < 0.05) and Gene Set Enrichment Analysis (GSEA). Atrasentan gene signature was cross-validated to transcriptome of kidney biopsy samples from IgAN patients (GSE141295 and GSE93798).

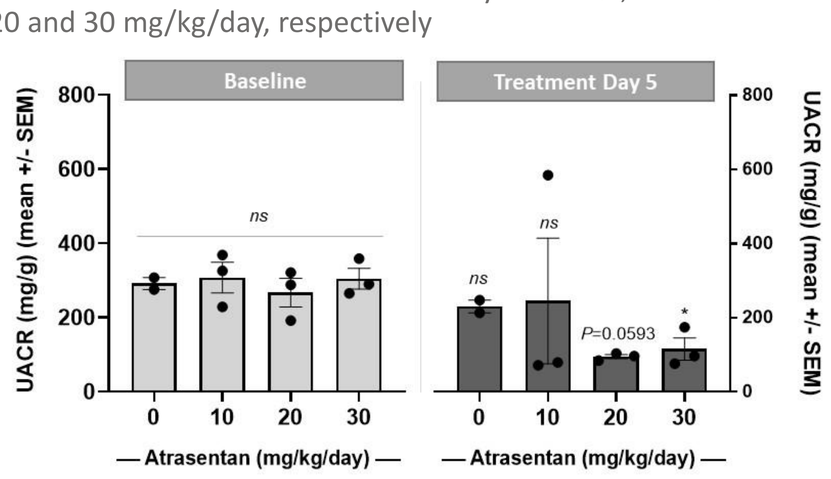
Results

1 Administered atrasentan doses

- Atrasentan dose = ([atrasentan] x 24 hr water consumption) / body weight
- The mean daily dose of atrasentan administered was 7.8, 16.0 and 29.0 mg/kg/day, in close approximation to the targeted doses of 10, 20 and 30 mg/kg/day respectively

2 Albuminuria

- At baseline, the gddY mice had substantial albuminuria, which was well matched across treatment groups
- Atrasentan reduced UACR from baseline by 28 ± 44%, 62 ± 8% and 63 ± 6% at 10, 20 and 30 mg/kg/day, respectively



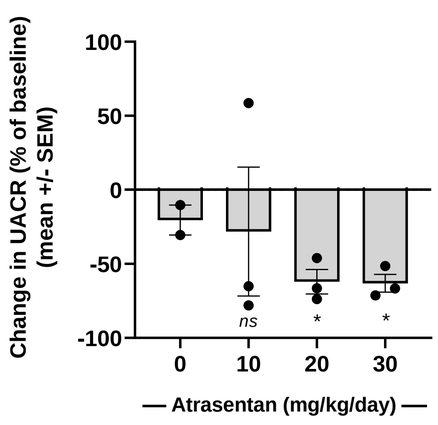


Figure 1: UACR in g-ddY mice, at baseline, prior to atrasentan administration, and following approximately 5 days of treatment with atrasentan at 0 (control), 10, 20 or 30 mg/kg/day in the drinking water (*P < 0.05 compared to baseline levels, paired t-test)

Figure 2: Change in UACR (% of baseline) in g-ddY mice, following approximately 5 days of treatment with atrasentan at 0 (control), 10, 20 or 30 mg/kg/day in the drinking water. (*P < 0.05 compared to control group (0 mg/kg/day), unpaired t-test)

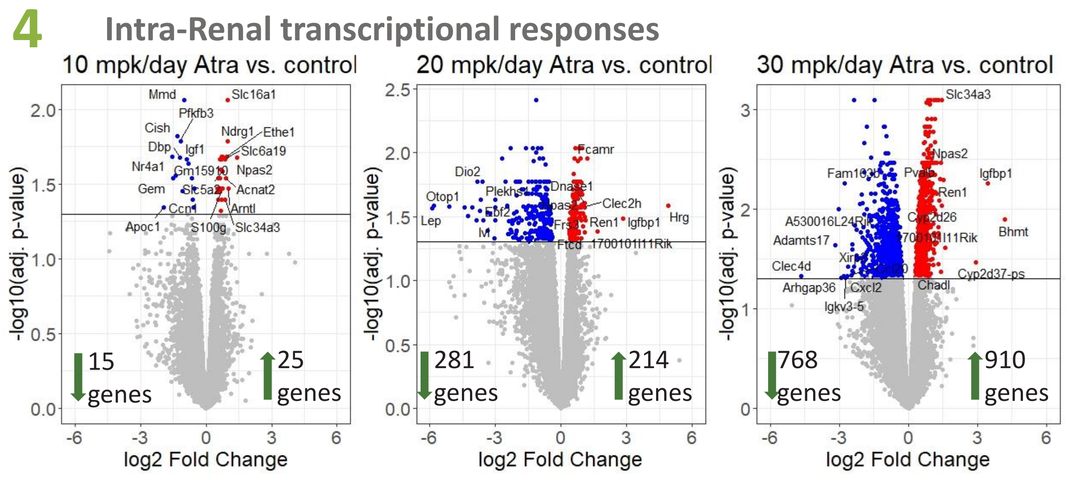
3 Plasma atrasentan concentrations

- Free (f) [atrasentan] plasma concentrations covered the ET_A *Ki* and were highly selective over ET_B, consistent with human exposures (0.75 mg qd)

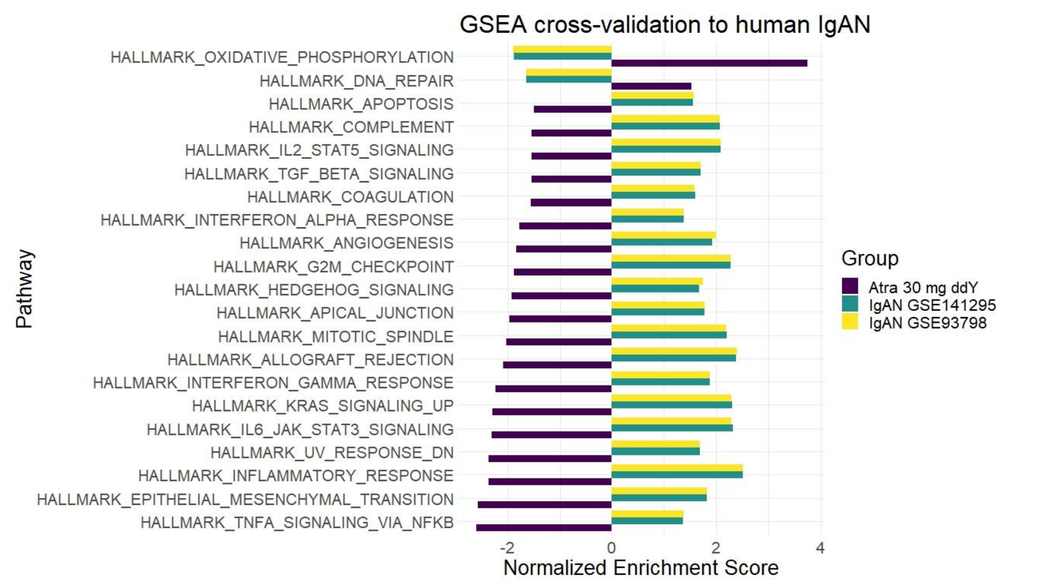
Dose (mg/kg/day)	f[Atrasentan] (pM)	Fold ET_A *Ki* (34 pM)	Fold ET_B *Ki* (63,300 pM)	ET_B Selectivity
10	90	2.6	0.0014	704
20	99	2.9	0.0016	642
30	207	6.1	0.0033	306

Results (Continued)

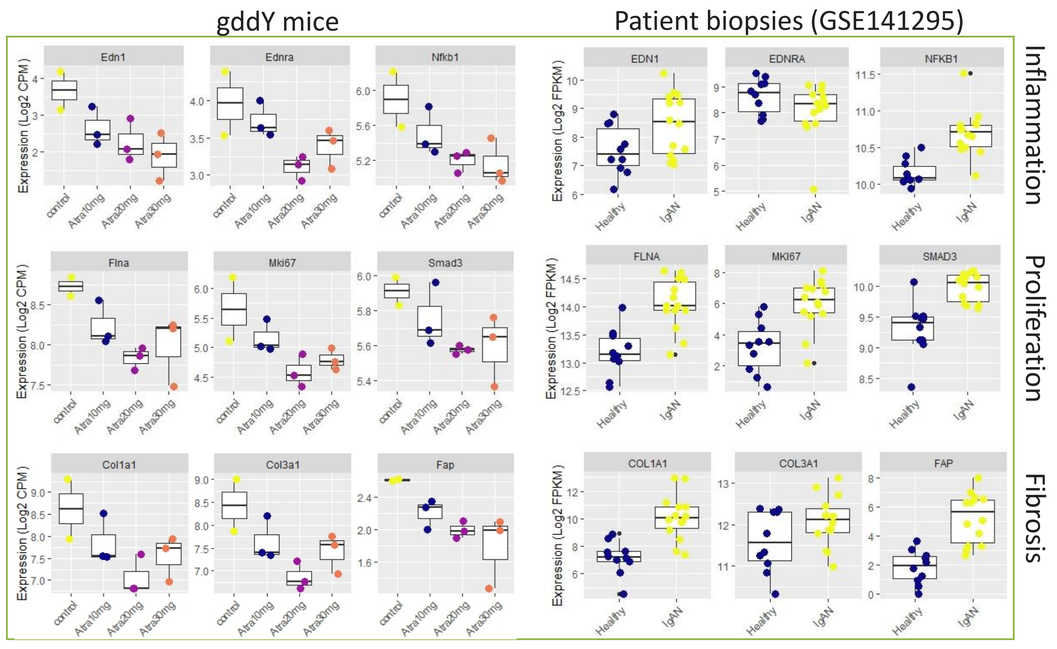
4 Intra-Renal transcriptional responses



- Dose dependence in differentially expressed genes



- GSEA showed that treatment of 30 mg/kg atrasentan in gddY mice reversed gene pathways found to be dysregulated in the glomeruli of IgAN patients



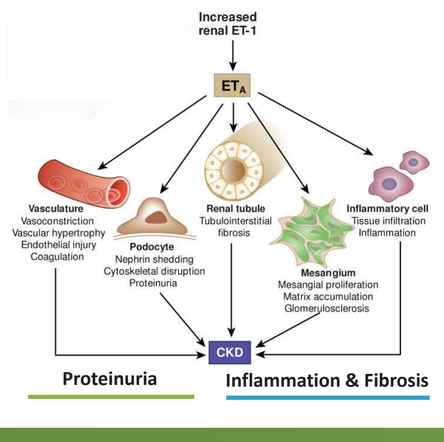
- Atrasentan downregulated driver genes in the proliferative, inflammatory, and fibrotic signaling pathways, and ET_A receptor target genes, reversing gene expression trends observed in IgAN patients

Conclusion

- Atrasentan, a potent and selective ET_A antagonist, leads to rapid reductions in albuminuria with intra-renal transcriptional downregulation of proliferative, inflammatory and fibrotic signaling in the gddY mouse IgAN model
- The dynamic transcriptional changes in the kidney, including downregulation of known direct ET_A receptor target genes, following only 5 days of treatment and prior to sustained long-term reductions in albuminuria and blood pressure that could mediate this benefit, is consistent with direct anti-inflammatory and antifibrotic effects of ET_A blockade in IgAN
- These results support further characterization of the effects of long-term treatment of atrasentan in the gddY mouse and support the therapeutic potential of atrasentan in IgAN to reduce proteinuria and kidney inflammation and fibrosis, key drivers of IgAN progression
- 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

ALIGN WCN21-0848

ClinicalTrials.gov Identifier: NCT04573478



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