TH-PO481

The NOX inhibitor setanaxib combined with ramipril reduces glomerular function decline and fibrosis in a mouse model of Alport syndrome

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INTRODUCTION

- Alport syndrome is a **rare genetic disorder,** typically presenting in **childhood or adolescence,** that is caused by variants affecting **type IV collagen proteins**
- These variants affect the integrity of basement membranes, resulting in **progressive kidney damage, hearing loss and vision problems**
- Setanaxib, an **inhibitor of ROS production** currently under investigation, **reduced inflammation and fibrosis** in preclinical models – mechanisms known to play a role in the progression of Alport syndrome

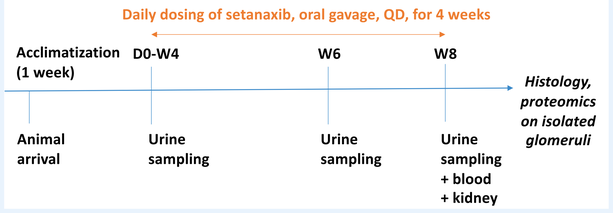
AIM

- To evaluate the **therapeutic potential of setanaxib** in Alport syndrome using a *Col4a3* KO mouse model

METHODS

- Four-week-old ***Col4a3* -/- KO male mice** (129/SvJ background)
- Administered one of the following regimens (n=10 per group) across a period of 4 weeks **(Fig. 1):**
  - Ramipril 10 mg/kg (in drinking water)
  - Setanaxib 60 mg/kg QD (by gavage)
  - Combination of setanaxib 60 mg/kg QD (by gavage) and ramipril 10 mg/kg (in drinking water)
  - Vehicle

Figure 1: Study design



RESULTS

Albuminuria

- Albuminuria and urine ACR increased between weeks 4, 6, and 8
- A **reduction in albuminuria** and **ACR** was observed at week 6 and 8 with ramipril monotherapy versus vehicle (statistically significant for ACR at week 8)
  - A **further reduction in albuminuria** and **ACR** was seen when setanaxib was combined with ramipril. The superior effect of the combination with setanaxib led to a robust, statistically significant reduction in albuminuria and ACR compared with the disease condition **(Fig. 2A, B)**
  - The combination of setanaxib and ramipril also led to a statistically significant reduction in **albuminuria and ACR** compared with ramipril monotherapy **(Fig. 3A, B)**
  - Setanaxib monotherapy did not significantly decrease albuminuria or ACR

Figure 2: (A) Urinary albumin concentration and (B) ACR at weeks 4, 6, and 8

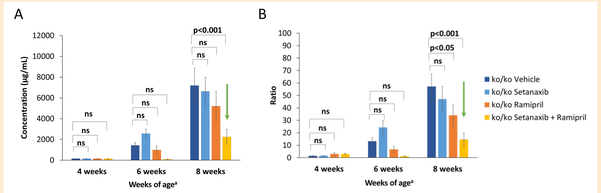
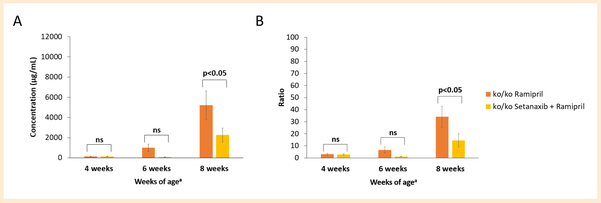


Figure 3: (A) Urinary albumin concentration and (B) ACR at weeks 4, 6, and 8 with setanaxib and ramipril versus ramipril alone



RESULTS (CONT.)

Fibrosis

- Histologic analysis indicated that the combination of setanaxib and ramipril **significantly decreased glomerular sclerosis**, which was further confirmed by Sirius red quantification of overall kidney fibrosis **(Fig. 4A, B)**

Figure 4A: PAS staining and pathologist score[b] – Glomerular sclerosis

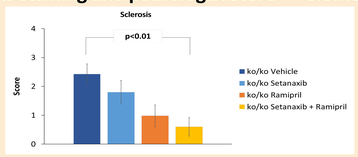
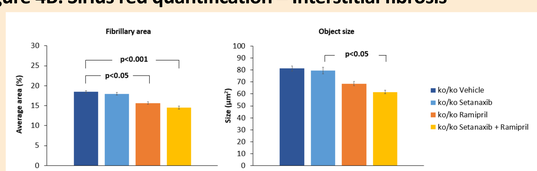


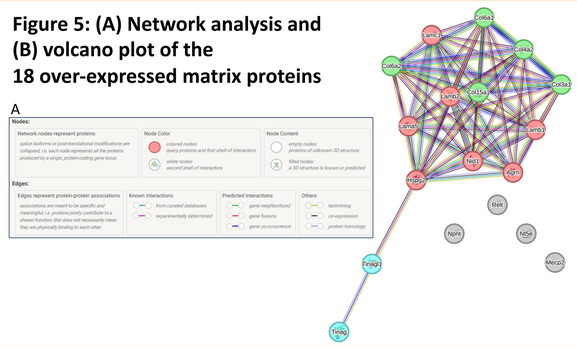
Figure 4B: Sirius red quantification – Interstitial fibrosis



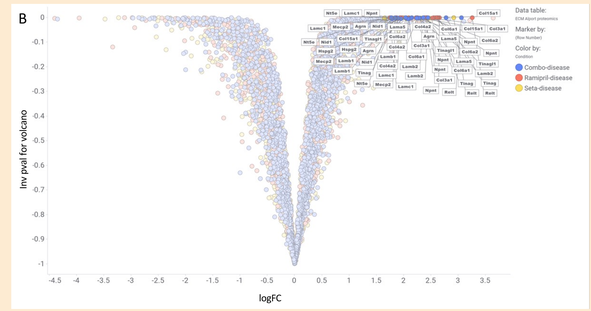
Proteomics

- Over-expression of only 18 matrix proteins was observed with all 3 active treatment regimens: setanaxib, ramipril, and combined setanaxib + ramipril (log2>1.5; p<0.01) **(Fig. 5)**

Figure 5: (A) Network analysis and (B) volcano plot of the 18 over-expressed matrix proteins



RESULTS (CONT.)



- *In silico* analyses demonstrated **increased detection of glomerular basement membrane and collagen proteins**, including laminin 521, perlecan, agrin, and dystroglycan, with a combination of setanaxib and ramipril

CONCLUSIONS

- **Setanaxib, when combined with ramipril, significantly reduced the decline in glomerular function and fibrosis** in a well-established mouse model of Alport syndrome through possible glomerular basement membrane rescue mechanisms

ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin/creatinine ratio; D, day; GAG, glycosaminoglycan; KO, knock-out; LG, laminin G-like domain G; LN, laminin N-terminal domain; NC1, non-collagenous domain; ns, not significant; PAS, periodic acid Schiff; QD, once-daily; ROS, reactive oxygen species; W, week.

Disclosures

TC: an employee of Calliditas Therapeutics. **MF, MM, and CL**: nothing to disclose. **RL**: Clinical trials principal investigator for Bayer, Calliditas, River3Renal, Travere; Consulting agreements: Calliditas, Purespring, Tribune; Collaborative research agreements: Calliditas, Four Points Innovation; Advisory board: Alport Syndrome Foundation, Alport UK.

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[a]Treatment started at 4 weeks.

[b]Pathologist conducting scoring was blinded to treatment.

Statistical comparisons were conducted as two-way ANOVA with Bonferroni's multiple comparisons test (post hoc test), except for interstitial fibrosis, where one-way ANOVA was conducted with Dunnett's multiple comparison test, and for glomerular sclerosis, where Kruskal–Wallis tests and Dunn's multiple comparison tests were conducted.