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) were 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

Albunminuria

- 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.

Histologic analysis indicated that the combination of setanaxib and ramipril had a further 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

Fibrosis

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

Proteomics

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

Figure 3: (A) Network analysis and (B) volcano plot of the 18 over-expressed matrix proteins

CONCLUSIONS

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

Disclosures

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

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