Nephroprotective effects of enalapril in the anti-GBM mouse model of glomerulonephritis

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Background & Aim

Translational rodent models of glomerulosclerosis are essential in drug discovery for chronic kidney disease (CKD). The anti-glomerular basement membrane (anti-GBM) model in mice represents a clinically relevant model as it exhibits key features of albuminuria and glomerulosclerosis.

This study aimed to investigate the effects of the angiotensin-converting enzyme inhibitor (ACEi) Enalapril on urinary biochemistry and renal histopathology in female mice with anti-GBM–induced glomerulosclerosis

Methods

See study outline. Female C57BL/6JRj mice (8 weeks) were randomized by body weight and dosed once daily from day –1. The vehicle was given orally, and Enalapril was provided ad libitum in drinking water (changed daily). Glomerulonephritis was induced by an intravenous injection of 100 µL anti-GBM serum administered on study days 1 and 2 (Groups 2 and 3). Control animals received PBS (Group 1). In study week 3, urine was collected in metabolic chambers (16h) for quantification of the urine albumin-to-creatinine ratio (uACR) and albumin excretion rate. At termination, the left kidney was weighed and processed for quantitative histological assessment of glomerulosclerosis (PAS), fibrosis (Col1a1) and macrophage infiltration (F4/80).

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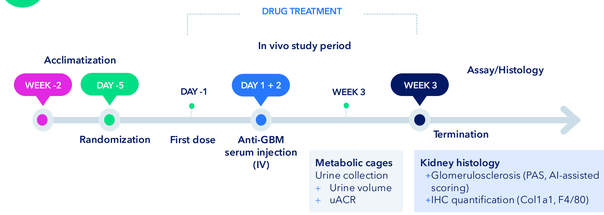
1 Study outline



Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing volume	Dosing concentration
1	Healthy control	Female	6	**Vehicle**	PO	Once daily	5 ml/kg	-
2	Anti-GBM - Vehicle	Female	10	**Vehicle**	PO	Once daily	5 ml/kg	-
3	Anti-GBM - Enalapril	Female	10	**Enalapril**	Drinking water	Ad libitum (changed once daily)	NA	**25 mg/kg**

2 Body weight profile

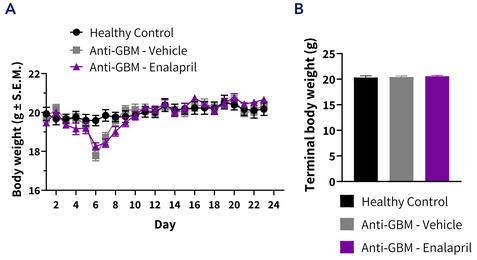


Figure 2. Enalapril **(A)** Body weight (profile plot). **(B)** Terminal body weight. Dunnett's test one-factor linear model. No differences at significance level 0.05. Data is shown as mean ± S.E.M.

3 Enalapril reduces albuminuria

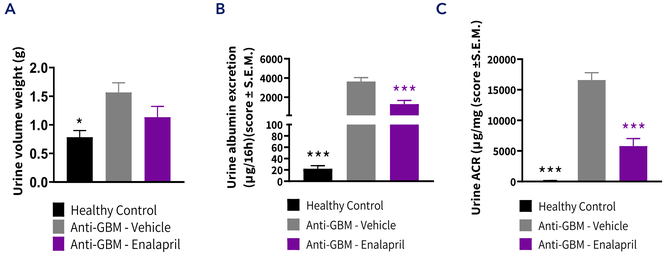


Figure 3. Enalapril reduces the albumin excretion rate and uACR. **(A)** Urine volume at week 3. **(B)** 16 hrs urine albumin excretion rate at week 3. **(C)** Urine ACR at week 3. *p<0.01, ***p<0.001 compared to Anti-GBM – Vehicle mice (Dunnett's test one-factor linear model). Data is shown as mean ± S.E.M.

4 Enalapril reduces glomerulosclerosis

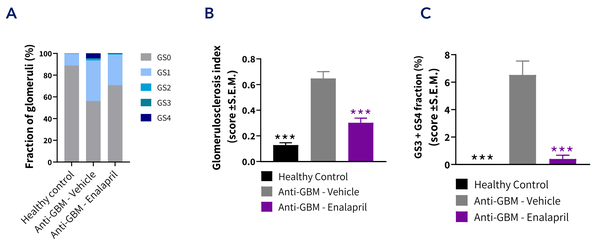
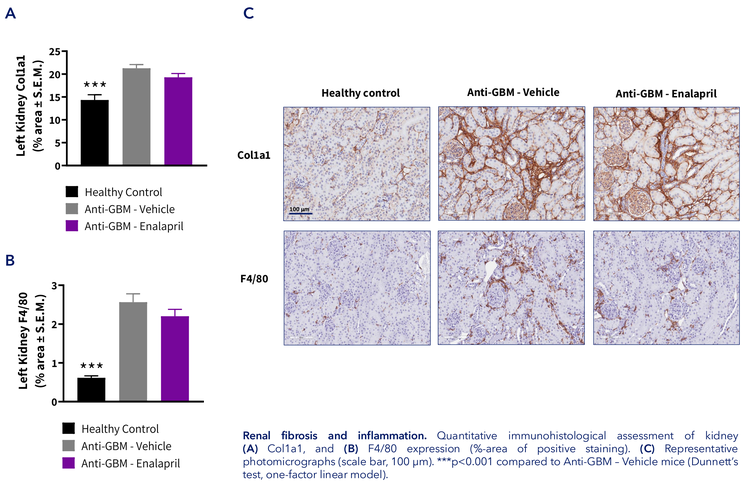


Figure 4. Enalapril reduces glomerulosclerosis index and GS3 +GS4 fraction.
(A) Glomerulosclerosis distribution. The percentage of animals with score 0 (normal), score 1 (up to 25% involvement), score 2 (up to 50% involvement), score 3 (up to 75% involvement) and score 4 (more than 75% involvement). **(B)** Glomerulosclerosis index (score ± S.E.M.) **(C)** Glomerulosclerosis score 3 and 4 (mean ± S.E.M.) **(D)** Representative photomicrographs (scale bar, 60 µm) showing severity of sclerosis (GS0-GS4) in affected glomeruli. From normal glomeruli (GS0) to global glomerulosclerosis (GS4). ***p<0.001 compared to Anti-GBM – Vehicle mice (Dunnett's test one-factor linear model).

5 Histological markers of renal fibrosis and inflammation



Renal fibrosis and inflammation. Quantitative immunohistological assessment of kidney **(A)** Col1a1, and **(B)** F4/80 expression (%-area of positive staining). **(C)** Representative photomicrographs (scale bar, 100 µm). ***p<0.001 compared to Anti-GBM – Vehicle mice (Dunnett's test, one-factor linear model).

Conclusion

The present study in female Anti-GBM mice establishes that 3 weeks of treatment with the ACEi; Enalapril:

+ Significantly reduces the urine albumin excretion rate and uACR
+ Significantly reduces glomerulosclerosis

These findings supports that the anti-GBM model is a preclinical relevant model to evaluate novel treatments for glomerulonephritis

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