P0348 **THE DUAL ENDOTHELIN ETA AND ANGIOTENSIN AT1 RECEPTOR BLOCKER SPARSENTAN PROTECTS AGAINST THE DEVELOPMENT OF ALBUMINURIA AND GLOMERULOSCLEROSIS IN THE GDDY MOUSE MODEL OF IGA.**

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Background and Aims: gddY mice are an IgA nephropathy (IgAN)-prone mouse model that develops albuminuria by 8 weeks (wks) of age with glomerular IgA, IgG, and C3 deposits and progressive mesangioproliferative glomerulonephritis. A previous study in the ddY mouse model, the more genetically heterogeneous predecessor of gddY mice, using the endothelin type A receptor (ET_AR) antagonist FR139317 resulted in amelioration of proteinuria and preservation of kidney function. Treatment of ddY mice with the angiotensin II type 1 receptor (AT_1R) blocker valsartan resulted in significant protection from glomerulosclerosis (GS) without a significant prevention in proteinuria. Here we examined the effect of sparsentan (SP), a dual ET_AR and AT_1R blocker, currently in phase 3 trials for focal segmental glomerulosclerosis and IgAN, on the development of albuminuria and GS in gddY mice.

Method: gddY mice at 4 wks of age were fed with control (C) chow (n=5) or chow containing 900 ppm (n=10) or 1800 ppm (n=10) SP (approximately 180 and 360 mg/kg/day) for 8 wks. Albuminuria (U-Alb) was assessed at 4, 6, 8, and 12 wks of age and plasma levels of SP were determined at 8 am and 4 pm at wks 6, 8, and 12. Kidney biopsies were taken at the end of the study at 12 wks of age for processing and 30 glomeruli per animal were scored for the percentage of GS.

Results: gddY mice fed SP in the diet for 8 wks from 4 wks of age demonstrated significantly ($*P<0.05$) decreased U-Alb compared to mice fed the C diet in a dose-dependent manner (Figure 1). The development of GS in mice fed the diet containing 1800 ppm SP was significantly ($*P<0.05$) attenuated compared to C diet (Figure 2). Plasma levels of SP taken at 8 am and 4 pm after 8 wks of treatment were (mean$\pm$SD) 281$\pm$107 and 105$\pm$62 ng/ml for 900 ppm SP respectively, and 774$\pm$674 and 304$\pm$176 ng/ml for 1800 ppm SP, respectively. Weight gain in mice fed SP was not different from mice that received C diet.

Conclusion: Eight weeks of treatment with SP attenuated increases in albuminuria and GS associated with the development of IgAN in gddY mice. If translated to the clinic, these data support SP as a new approach to the treatment of IgAN.