Abstract Title:

Dual blockade of endothelin A and angiotensin II type 1 receptors with sparsentan is protective in the gddY mouse model of IgA nephropathy to a greater extent than losartan

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Abstract Body

Background and Aims:

The mechanism for the development of IgA nephropathy (IgAN) is not completely clarified. gddY mice are an IgAN-prone model. Endothelin (ET) type A receptor (ET_AR) antagonist reduced the risks of renal events in patients with diabetes and chronic kidney disease (CKD). Sparsentan (SP) is a novel, highly selective, first-in-class, single-molecule Dual Endothelin Angiotensin Receptor Antagonist (DEARA) being developed for the treatment of focal segmental glomerulosclerosis and IgAN and recently received accelerated approval in United States for the reduction of proteinuria in adults with IgAN at high risk of disease progression.

To compare dual antagonism of ET_AR and AT_1R using SP with the monoselective AT_1R antagonist, losartan (LS) in a model of IgAN we examined the effect of treatment in gddY mice, on the development of renal injury at doses resulting in similar blood pressure lowering.

Methods:

gddY mice at 4 wks of age were treated for 8 or 16 wks with control chow (C; n=10), chow containing SP at 900 ppm (SP900; n=12), or with C and LS in drinking water to deliver 30 mg/kg of LS (LS30; n=12). Systolic blood pressure (BP) was measured by tail-cuff plethysmography at 8, 12, and 18 wks of age. Albuminuria/creatinine ratio (ACR) was assessed every two wks until 20 wks of age. Kidney biopsies were taken from a sub-set of mice sacrificed at 12 wks of age (4-5 per group) and at the end of the study at 20 wks of age (5-7 per group). The biopsies were processed for determination of the percentage of glomerulosclerosis (GS), the number of podocytes with WT-1 positive cells, and measurement of the glycocalyx (GC) area using FITC-labeled lectin.

Results:

Despite the similar systemic hemodynamic effects in SP900 and LS30 mice, the reduction in ACR from baseline was more rapid in SP900 mice compared to LS30 mice. The reduction in ACR from baseline in SP900 mice was significantly greater than in C and LS30 mice at 8 wks of age. At 12 wks of age the change in ACR from baseline was significant from C in SP900 and LS30 mice and also between SP900 and LS30. Development of GS was significantly attenuated in mice at 20 wks of age treated with SP900 compared to those treated with C, but not in LS30 mice. Furthermore, whereas compared to treatment with C at 20 wks of age, SP900 and LS30 significantly attenuated the reduction in podocyte number ($P<0.001$ and $P<0.05$ respectively), the podocyte protection with SP900 was significantly greater compared to LS30. Notably SP900 but not LS30 mice also ameliorated the loss in GC area. Thus, SP treatment delayed development of renal injury to a greater extent than losartan. Notably expression of mRNA for ET-1, ET_AR, and AT_1R and proinflammatory genes were upregulated in gddY mice at 12 wks was prevented by SP and LS to a comparable extent.

Conclusion:

Treatment of gddY mice from 4 to 20 wks of age with SP resulted in a rapid and significant reduction in ACR and attenuation of GS, loss of podocytes and GC damage to a greater extent than treatment with LS despite equivalent lowering of BP. These results in gddY mice suggest that the effects of SP are beyond those mediated through reduction in systemic BP supporting the hypothesis that the usage of SP results in a more efficacious therapeutic than an angiotensin receptor blocker alone in preventing the development of renal injury in IgAN.