EPOETIN BETA PEGOL ALLEVIATES TUBULAR IRON OVERLOAD THEREBY MITIGATING EXACERBATION OF RENAL DAMAGE IN RATS WITH GLOMERULAR DISEASE

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Introduction and Aims: The increased deposition of iron in the kidneys that occurs with glomerulopathy hinders the functional and structural recovery of the tubules and promotes progression of chronic kidney disease (CKD). Epoetin beta pegol (continuous erythropoietin receptor activator, C.E.R.A.) strongly suppresses plasma hepcidin-25 (hep-25) levels and has a long half-life in blood. We showed previously that C.E.R.A. exerts a renoprotective effect and slows CKD progression accompanied by alleviation of iron contents in kidney, but the causal relationship remained unclear.

Methods: A rat model of chronic progressive glomerulonephritis (cGN) was established by intravenous injection of anti-Thy1.1 monoclonal antibody (OX-7; 0.6 mg/kg) to unilaterally nephrectomized rats (F344, male). The next day (Day 1) or Day 14 after the induction of kidney disease, cGN rats were intravenously administered a single dose (25 µg/kg) of C.E.R.A. (cGN+C) or vehicle (disease-control rats, cGN+V).

Results: urinary protein excretion (uTP) levels in cGN rats were increased at 1 wk and decreased at 2 wks but did not completely return to normal range. uTP later became elevated again, and kidney function declined into end-stage renal disease at 20 wks (CCr in cGN rats was 19.8% of CCr in Sham rats [sham-operated without OX-7]). The decline in CCr at 20 wks was suppressed by a single dose of C.E.R.A. given on Day 1 but not on 2 wks (Day 1: 60.5% of CCr in Sham rats; 2 wks: 23.2%). Therefore, C.E.R.A. treatment of initial renal insult might be effective in delaying CKD progression in this model. In cGN rats, kidney iron content significantly increased (Day 1: 39.5 ± 0.9 µg/g; Day 4: 47.1 ± 0.6 µg/g; p<0.05) and urinary L-FABP was significantly elevated (Sham Day 1: 5.5 ± 0.3 ng/day; cGN+V Day 1: 160 ± 14.4 ng/day; cGN+V Day 4: 393.7 ± 30.7 ng/day; p<0.05). The iron accumulation might be partly due to elevated urinary iron excretion (cGN+V Day 1: 1.5 ± 0.2 µg/day; Day 4: 7.7 ± 0.7 µg/day; p<0.05) and changed expression of iron transporters (up-regulated DMT-1 mRNA and down-regulated FPN mRNA in kidney at Day 1). By contrast, a single dose of C.E.R.A. at Day 1 mitigated iron deposit in the kidney (Day 8: cGN+V, 55 ± 2.5 µg/g; C.E.R.A., 37.5 ± 1.5 µg/g; p<0.05) through continual hep-25 suppression until Day 8, but did not alleviate elevated urinary iron excretion. From Day 14 to 28, cGN rats showed increased tubular dilation, whereas C.E.R.A. mitigated this structural damage together with a significant lowering of iron content and urinary L-FABP at Day 28. There was significant correlation between kidney iron content and urinary L-FABP at Day 28.

Conclusions: A single dose of C.E.R.A. could mitigate exacerbation of kidney damage thereby delaying CKD progression in rats with glomerulonephritis. Alleviation by C.E.R.A. of the exacerbation of kidney dysfunction associated with structural tubular damage could be attributed to the lowering of tubular iron deposition in the initial phase of kidney disease partly due to inhibition of continually elevated hepcidin-25.