2-O-059 Oral Sessions

Modulistat, a PHD inhibitor, ameliorated erythropoiesis in adenine-induced nephropathy mice

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Aim: Erythropoietin (EPO) is essential for the hematopoiesis. Kidney is the major organ to produce EPO in adults, so that kidney damage reduces its level in the body, resulting in anemia. Hypoxia-inducible factor is a well known translational factor to induce adaptive responses in the cell, and plays significant role on the EPO gene translation in the EPO producing cells. Therefore, the inhibitors of prolyl hydroxylase domain-containing protein (PHD) is awaited for one of the new therapeutic strategies against renal anemia. Likewise, it can be predictable that tons of patients who receive the PHD inhibitor have renal dysfunction as a cause of anemia, while the potential reno-protective effects of PHD inhibitor have not been evaluated well. In the present study, we investigated the effects of modulistat, a PHD inhibitor, on anemia and renal dysfunction when initiated after the onset of adenine-induced nephropathy.
Methods: Male C57Bl/6J mice received adenine orally for the induction of nephropathy. After the onset of nephropathy, the mice were separated into 2 groups and received either vehicle or modulistat (3 mg/kg/day, p.o.) for 4 weeks.
Results: There was no difference in hematocrit level between vehicle- and modulistat-treated groups (34.8±0.9 vs. 34.8±0.6%). At 4 weeks of the administration, vehicle-treated mice showed significant anemia (hematocrit level: 28.5±1.0%), and modulistat ameliorated the anemia (44.3±1.4%). Vehicle-treated mice exhibited reduction of creatinine clearance and body weight, increase in blood urea nitrogen, progressed histopathological changes, immune cells infiltration and dehydration. Modulistat improved immune cells infiltration and dehydration but not the other parameters.
Conclusion: Modulistat treatment after the onset of nephropathy could recover mice from anemia. Modulistat improved some parameters of renal abnormality but unable to restore the renal function.