Pharmacokinetics and long-term renal effects of ciclosporin A in a pig model

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ABSTRACT

CsA is still widely used in the immunosuppressive management of organ transplantation and some immunomediated diseases despite the introduction of novel immunosuppressant drugs. The long-term treatment of CsA is, however, limited by several serious side effects, especially chronic CsA nephrotoxicity, which has been extensively examined in a salt-depleted rat model. Nevertheless, this model has major disadvantages due to significant differences in anatomy, physiology, and pathophysiology to humans.

The central aim of this PhD thesis was to develop a human-related model of chronic CsA nephrotoxicity. For this reason we investigated pharmacokinetics and long-term renal effects of CsA in a porcine model. Moreover, we aimed to evaluate the potential renoprotective role of angiotensin II receptor blockade on chronic CsA-induced nephropathy in the pig.

We found that pigs have lower volume of distribution at steady state and elimination half-life of CsA as compared to renal transplant patients. The total clearance in pigs is, however, essentially the same, which yields comparable area under concentration versus time (AUC) after equivalent intravenous CsA dose in pigs and renal transplant patients. On the contrary, pigs require higher doses of CsA Neoral formulation in order to obtain comparable AUC values after oral CsA administration as in renal transplant patients, probably due to its lower bioavailability.

We also demonstrated that long-term CsA treatment (10 mg/kg/day for 12 months) causes interstitial fibrosis and glomerulosclerosis in the porcine kidney similar to those observed in humans. Furthermore, long-term CsA administration results in renal enlargement, which precedes the histopathological changes and, thus, may represent an early stage of chronic CsA nephrotoxicity in pigs. Telmisartan attenuates the histopathological changes and tends to provide late preventive effect on renal enlargement. Importantly, telmisartan does not impair renal function in pigs.

In conclusion, the pig is a useful preclinical model of chronic CsA nephrotoxicity. Our results in this human-related animal model indicate that angiotensin II receptor blockade may have potential clinical applications to prevent chronic CsA nephrotoxicity. If verified in humans, this would improve long-term renal and other organ transplant survival and prevent CsA nephrotoxicity in patients with immunomediated diseases treated with CsA.