KSN 2017 Abstract

KSN-17-P160

Effect of Conversion to Belatacept on Tacrolimus-Induced Diabetes Mellitus in Rats.

Long JIN, Jian JIN, Kang LUO, Sun woo LIM, Byung ha CHUNG, *Chul woo YANG

Transplant Research Center, The Catholic Universit, Convergent Research Consortium for Immunologic Disease, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea, Korea,South

Objectives : Belatacept is a promising immunosuppressant for replacing calcineurin inhibitors (CNIs), but its effect on CNIs-induced diabetes mellitus (DM) is not adequately studied. We tested the effect of conversion to belatacept on tacrolimus-induced DM.

Methods : Two separate experiments performed. The first experiment was conducted to determine diabetogenicity of belatacept. We administered five doses of belatacept (0.25, 0.5,1, 2 and 4 mg/kg) via tail vein injection at the weekly basis for four weeks. The second experiment was conversion study. After inducing tacrolimus-induced DM with three weeks treatment with tacrolimus (TAC), TAC was converted to belatacept (1 and 2 mg/kg) for three additional weeks. The effect of belatacept on TAC-induced pancreatic islet dysfunction was evaluated by an intraperitoneal glucose tolerance test (IPGTT), HbA1c, plasma insulin level, islet size and glucose-stimulated insulin secretion (GSIS). The influence of oxidative stress was evaluated by measuring markers of oxidative stress 8-hydroxy-2`-deoxyguanosine (8-OHdG) and antioxidant enzyme maker of manganese superoxide dismutase and heme oxygenase-1 (MnSOD) in pancreas tissue sections. To determine whether belatacept has preserve effects, we also measured cell viability AO/PI staining in isolated rat islets.

Results : Interestingly, the first experiment showed that treatment with belatacept showed similar blood glucose level compares with VH group. More importantly, belatacept 1 and 2 mg/kg showed healthier blood glucose level than VH groups. However, there was no difference between the other groups and time course. From the first study, we found that 1 and 2 mg/kg of belatacept have a clinically relevant therapeutic level. As expected, conversion from TAC to belatacept groups (belatacept 1mg/kg and 2mg/kg) improved TAC-induced pancreatic beta-cell dysfunction compared with the TAC and TAC withdrawal groups. The IPGTT and HbA1c showed conversion to belatacept has more significantly decreased blood glucose level and HbA1c

level than TAC withdrawal or TAC treatment alone. Consistently, plasma insulin level showed higher in conversion to belatacept groups than TAC withdrawal or TAC treatment alone. Conversion groups recovered islet size and GSIS which was significantly decreased in TAC and TAC withdrawal group. TAC treatment increased the level of 8-OHdG and reduced the level of MnSOD, and conversion could recover this effect. An ex vivo study of AO/PI staining showed that TAC treatment increased pancreas beta cell death. However, conversion to belatacept effectively decreased TAC-induced islet cell death.

Conclusions : Our study indicated that conversion to belatacept is useful and provides a rationale for the conversion to belatacept on TAC-induced DM.

Keywords : Belatacept; CTLA4Ig; Tacrolimus; Diabetes