KSN 2018
Seoul, Korea · May 17 - 20

Abstract Type : Poster
Presentation No. : PDO 003

Comparison of Diabetogenic Effect of Tacrolimus and CTLA4Ig in Streptozotocin-induced Diabetes Mellitus in Rats

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Objectives:

We recently reported that CTLA4Ig conversion is effective in tacrolimus (TAC)-induced diabetes mellitus (Transplantation, 2018 Jan 10), but it is not clear whether CTLA4Ig is working is diabetic condition. In this study, we compared the diabetogenic effect of TAC and CTLA4Ig in experimental model of streptozotocin (STZ)-induced diabetes mellitus (DM) in rats.

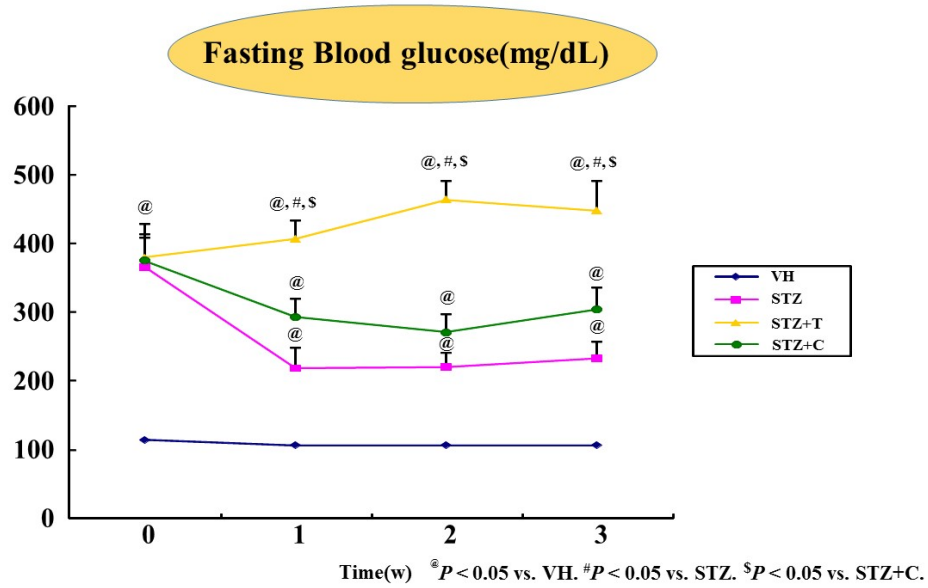
Methods: Experimental model of diabetes mellitus was induced by injecting STZ at a dose of 60 mg/kg via tail vein. After establishment of diabetes mellitus, rats were randomly assigned as TAC (1.5 mg/kg per day, subcutaneously, n=27) or CTLA4Ig (2 mg/kg once a week, tail vein injection, n=9) for 3 weeks. Control group was treated with vehicle (n=9). The effect of TAC or CTLA4Ig on STZ-induced diabetes mellitus was evaluated by assessing fasting blood glucose level, body weight, survival rate.

Results: The TAC and CTLA4Ig treatment group showed significantly increase of blood glucose levels compared to the STZ-induced DM group at 3weeks (STZ: 233 ± 23 mg/dL, STZ+TAC: 448 ± 43 mg/dL, STZ+CTLA4Ig: 304 ± 32 mg/dL, $P<0.05$, vs. STZ), but CTLA4Ig treatment significantly decreased the blood glucose level compared with the TAC group at 3weeks.The STZ-induced DM group significantly reduced body weight compared to the VH group at 3weeks (Δ body weight: VH: -0.4 ± 24.2 g, STZ: -74.4 ± 26.8 g, STZ+TAC: -93.6 ± 29.6 g, STZ+CTLA4Ig: -90.1 ± 33.5 g, $P<0.05$, vs. VH), but TAC and CTLA4Ig treatment group was no significantly increase or decrease body weight compared with the STZ-induced DM group. The 21days survival rate of the TAC treatment group was only 55.6% compared with the other groups. Namely CTLA4Ig groups ameliorated blood glucose level, survival rate compared to the TAC groups.

Conclusions:

CTLA4Ig is effective in STZ induced diabetes mellitus. This finding provides the rationale for use of CTLA4Ig in diabetic patients.

Fasting Blood glucose



$^{@}P < 0.05$ vs. VH. $^{\#}P < 0.05$ vs. STZ. $^{\$}P < 0.05$ vs. STZ+C.

Survival rate