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Effect of conversion from tacrolimus to CTLA4Ig in experimental model of diabetes mellitus

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Objectives: CTLA4Ig is a promising alternative to calcineurin inhibitors. We investigated the effect of conversion from tacrolimus (TAC) to CTLA4Ig in an experimental model of diabetes mellitus (DM).

Methods: Experimental model of DM was induced by streptozotocin (STZ). We administered TAC (STZ+T group, 1.5 mg/kg, daily) or CTLA4Ig (STZ+C group, 2 mg/kg, weekly) for 6 weeks or TAC for 3 weeks and then converted to CTLA4Ig for additional 3 weeks (STZ+TC group). STZ-induced diabetic rats were used as control (STZ group). The effect of conversion was evaluated by fasting blood glucose (FBG) level, hemoglobin A1c (HbA1c), histopathology of pancreas islets, oxidative stress levels, macrophage infiltration, and apoptosis.

Results: TAC treatment in diabetic rats significantly increased FBG and HbA1c levels, but conversion to CTLA4Ig decreased these levels. The STZ+T group revealed decreased pancreatic islet size and insulin granule number compared to the STZ group, but conversion to CTLA4Ig restored both parameters. The STZ+T group showed significantly increased oxidative stress (increased 8-OHdG and decreased MnSOD) in pancreatic islets compared with the STZ group, but it was decreased in the STZ+TC group. The number of ED-1 positive cells in the STZ+T groups was higher than the STZ group and was reduced in the STZ+TC group. The increased TUNEL-positive cells or active caspase-3 expression in the STZ+T group was reduced in the STZ+TC group.

Conclusions: Conversion to CTLA4Ig from TAC is effective in a diabetic model. This finding provides the rationale for use of CTLA4Ig in TAC-treated diabetic patients.