5.10 Effects of CD8+CD28- T suppressor lymphocyte (Ts) on B- and T-lymphocyte function in systemic lupus erythematosus (SLE)

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Aims: The function of Ts has previously been suggested to be defective in patients with SLE. In this study, we investigated the suppressive activity of freshly isolated, highly purified CD4+CD28- Ts from patients with SLE on B- and T-lymphocytes.

Methods: Peripheral CD8 cells from patients with SLE were isolated by negative selection with anti-CD4, CD4 and CDl9 Dynabeads. CD8+CD28- cells were purified by removing CD28+ subset of cells by anti-CD28 monoclonal antibody labelling followed by the addition of anti-rat lgG Dynabeads. Purified CD8+CD28- Ts were then cultured alone, with ConA, TGFß or histamine for 2 days. Culture supernatants were then added to responder peripheral blood mononuclear cells (PBMC) from healthy subjects or another patient with SLE for detection of suppressive activity on B- and T-lymphocytes. For B-cell activity, PBMC were activated with PWM and the production of lgG was measured after 7 days. For T-cell activity, PBMC were stimulated with PHA and cell proliferation was measured by thymidine incorporation after 3 days. Results were compared with controls.

Results: Ts from SLE patients and control subjects had no inhibitory effects on T-cell proliferation. Supernatants of Ts which were cultured alone or with TGFß or histamine did not influence IgG production of responder B-cells. Supernatants of control and SLE Ts which were ConA stimulated significantly decreased the lgG production of healthy subject derived responder B-cells by 63.4 (±35.6)% and 45.2 (±39.9)% respectively (controls vs SLE, p=0.2). However, if the responder B-cells were derived from patients with SLE, no lgG inhibitory effects were demonstrated.

Conclusion: ConA was a critical stimulant of Ts. Ts had no suppressive activities on T-cell proliferation. Suppressive effects of Ts from patients with SLE on normal B-cells were intact. However, the same Ts failed to suppress the production of IgG by SLE B-cells. Further studies on the cytokine profile of the Ts supernatants, Ts-B interaction and B cell activity in SLE are currently underway.

5.11 Tacrolimus as primary prophylactic immunosuppressive therapy after renal transplantation

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To study the safety and efficacy of tacrolimus (FK506) as primary prophylactic therapy after cadaveric renal transplant, 11 consecutive recipients of the first cadaveric renal transplant were recruited prospectively into the study after informed written consent. All but one patients were put on sequential immunosuppressive therapy comprising anti-thymocyte globulin, prednisolone, azathioprine at standard doses and tacrolimus (0.2 mg/kg/day). The dosage of tacrolimus was adjusted to achieve a whole-blood trough level (IMx and IMx2, Abbott Laboratories, Germany) of 10-15 ng/mL over the initial 3-month period and 8-12 ng/mL afterwards. One patient was excluded from the study because of the development of post-operative delirium after transplant. Ten patients with a mean age of 44.7±6 years were followed up for 136 patient-months. The mean HLA mis-matches and cold ischemic time were 3.2±1.2 and 10.9±2.5 hours respectively. One patient was converted to cyclosporin at week-16. Patient and graft survival rate at l-year were both 90%. The mean serum creatinine level at 1-year after transplant was 129±6 ,µM. The mean dose of tacrolimus increased from 0.2 mg/kg/day to 0.31±0.12 mg/kg/day at 4-week and then decreased to 0.13±0.11 mg/kg/day at 52-week post-transplant. The mean tacrolimus whole-blood trough level at l-week, 4-week and 52-week post-transplant were 7.83±5.37 ng/mL, 10.7±3.54 ng/mL and 6.05±2.7 ng/mL respectively. 6/10 (60%) of the patients suffered from early acute graft rejections (<6 weeks after transplant) and 1/10 (10%) had an episode of rejection at 16-week after transplant. Only 2/7 (28%) rejection episodes were biopsy-proven and all the rejections were controlled by pulse methylprednisolone therapy. The median tacrolimus whole-blood trough level at the time of rejection was 7.1 ng/mL (range: <5 to 13.4 ng/mL) that was well below the recommended therapeutic level. Cytomegalovirus infection and herpes simplex infection developed in 2 (20%) and 3 (30%) patients respectively 1/10 (10%) patient had Kaposi's Sarcoma at 15-week after transplant. 2/10 (20%) patients developed diabetes mellitus and the mean cholesterol level increased from 5.05±1 mM to 5.57±1.5 mM after transplant. We conclude that tacrolimus is an effective prophylactic immunosuppressive agent after renal transplant but further refinement in the immunosuppressive regime and dosage is probably necessary.