RENAL TRANSPLANTATION. CLINICAL - 1

FP886 T REGULATORY CELL THERAPY TO CONTROL INFLAMMATION IN RENAL ALLOGRAFTS

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Introduction and Aims: The presence of inflammatory cellular infiltrate in renal allografts on protocol biopsies is associated with progressive renal dysfunction. 10-20% of patients on CNI-based regimens exhibit cellular inflammation below the threshold for a Banff-based diagnosis of rejection. Control of cellular responses without intensifying immunosuppression drug therapy with T regulatory cells infusion(s) may provide more desirable protection from alloimmune responses without the risk of drug toxicities. A pilot study to infuse ex vivo expanded polyclonal T regulatory cells in patients with cellular inflammation in renal allografts is underway at the University of California, San Francisco. We present the first case treated with this novel protocol.

Methods: Peripheral blood CD4+CD25+CD127lo Tregs were isolated using fluorescence activated cell sorting. The purified Tregs were expanded ex vivo for two weeks using two rounds of anti-CD3/anti-CD28 stimulations plus IL-2. The expansion medium contained deuterated glucose to label Tregs for pharmacokinetics assessment post-infusion. The first patient enrolled in this study was found to have mild to moderate inflammation (Banff i1,t1) in his 6-month protocol biopsy. He received a single infusion of 320 x 10^6 Tregs. Levels of infused Tregs in the peripheral blood were determined by measuring deuterium enrichment using gas chromatography and mass spectrometry. Graft inflammation is reassessed in a repeat biopsy 2 weeks after Treg infusion. Patients were monitored clinically for infusion reactions, infection, and renal function.

Results: One patient with Banff i1, t1 inflammation and normal renal function has received Treg infusion to date. This patient is a recipient of a living-related kidney transplant who had basiliximab induction and was maintained on tacrolimus, MMF, and prednisone. He had a lower yield of Tregs due to a low percentage of Tregs among CD4+ cells when compared to healthy controls and other non-transplant patients. Tregs expanded 311 fold and met all release criteria for infusion. Infused Tregs peaked on day 7 after administration and represented 4% of all Tregs in the peripheral blood at that time point. He did not experience any infusion related reactions. Repeat kidney biopsy at 2 weeks post Treg infusion showed no inflammation. The patient had transient lymphopenia (50% decrease in lymphocyte count, CD3+, CD4+ and CD8+ cells) that started 4 days and resolved 28 days post Treg infusion. No infections were reported and he maintained stable graft function at the most recent follow-up at 2 months after infusion.

Conclusions: It is feasible to isolate and expand Tregs from transplanted patients on immunosuppression. The pharmacokinetics of infused Tregs is similar to that seen in non-immunosuppressed patients. The treatment was well tolerated and at least in one case, prompt clearance of the inflammation occurred soon after the Treg infusion. Whether the decrease in T cell subsets was due to a Treg mediated T cell depletion in unclear. If confirmed these observations may suggest a therapeutic role for Tregs in transplantation.

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