Immune Alteration in Stable Renal Allograft Recipients Treated with Belatacept

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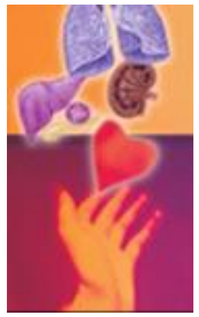

Background

In the recent BENEFIT trials, selective costimulation blockade with belatacept resulted in improved renal allograft function compared to cyclosporine, but a higher incidence of early acute rejection episodes and post-transplant lymphoproliferative disease (PTLD). The specific effects of long-term therapy with belatacept on immune phenotype are unknown.

Purpose

Characterize T cells in kidney recipients to examine effects of belatacept on:

-overall immune phenotype

-viral-specific immunity

Methods

-Cross-sectional study

Groups:

1. Healthy, untreated controls
2. Kidney recipients treated with **tacrolimus**
3. Kidney recipients treated with **belatacept**
4. Transplant candidates on hemodialysis

Analysis:

Polychromatic flow cytometric characterization of lymphocyte phenotype

-Memory, activation, exhaustion

-EBV and CMV-specific T cells

Table 1. Subject Demographics

Group	Treatment	Number (n)	Age (years)	Sex (M/F)	# months s/p txp
Healthy Controls	None	10	43.8	5 / 5	n/a
Tacrolimus (>6m s/p kidney txp)	**Tacrolimus** + MMF + Prednisone	9	47.9	6 / 3	51.7
Belatacept (>6m s/p kidney txp)	**Belatacept** + MMF +Prednisone	10	51.1	4 / 6	92.2
Dialysis (no h/o transplant)	None	6	47	2 / 4	n/a

Results

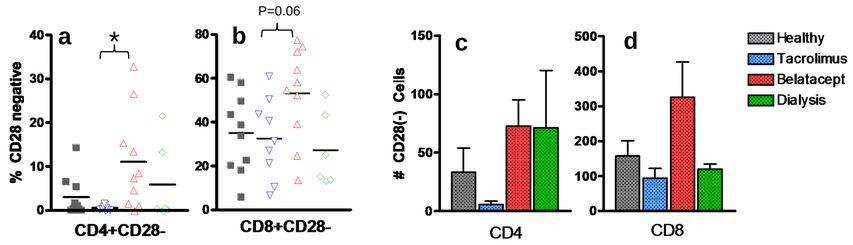

Figure 1. Treatment with belatacept results in increased frequency / absolute number of CD28(-) T cells. Patients treated with belatacept experienced an increase in the frequency and number of (a,c) CD4+ CD28(-) and (b,d) CD8+CD28(-) T cells, which was significantly greater than patients treated with tacrolimus. *p<0.05 (1-way ANOVA). Bars represent SEM.

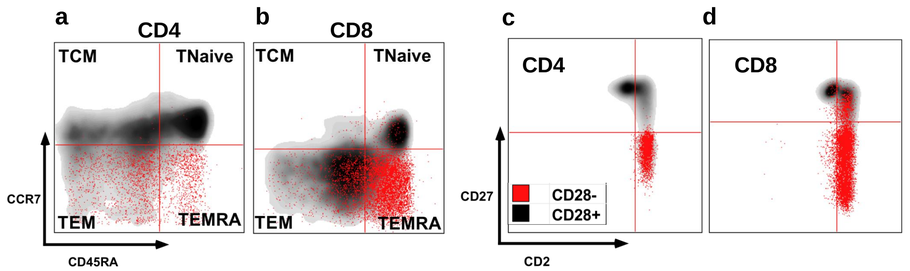

Figure 2. CD28(-) T cells express markers of activation and terminal memory differentiation. CD28(-) cell populations in all study groups were more likely to express markers of effector and effector-RA memory (a,b), high levels of CD2, and decreased CD27 (c,d). Representative plots gated on bulk CD4 and CD8.

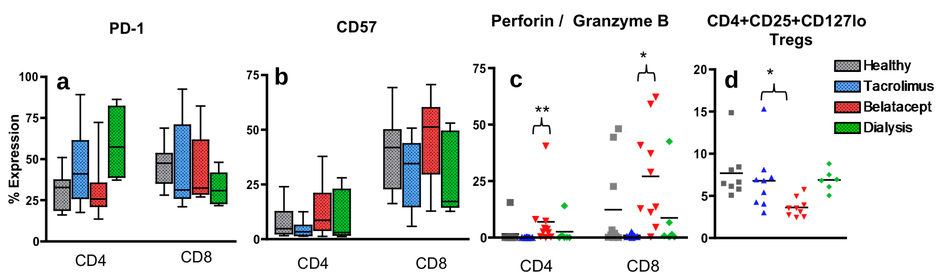

Figure 3. Belatacept-treated subjects demonstrate a more senescent phenotype, increased secretory granule production and lower Treg frequency. Despite similar expression of the exhaustion marker PD-1 (a), belatacept-treated subjects had a higher frequency of CD4 and CD8 T cells expressing the senescence marker CD57 (b) and the secretory granules perforin and granzyme B (c). There was a lower frequency of peripheral Tregs (defined by surface markers CD25 and CD127) in subjects treated with belatacept (d). *p<0.05 **p<0.01

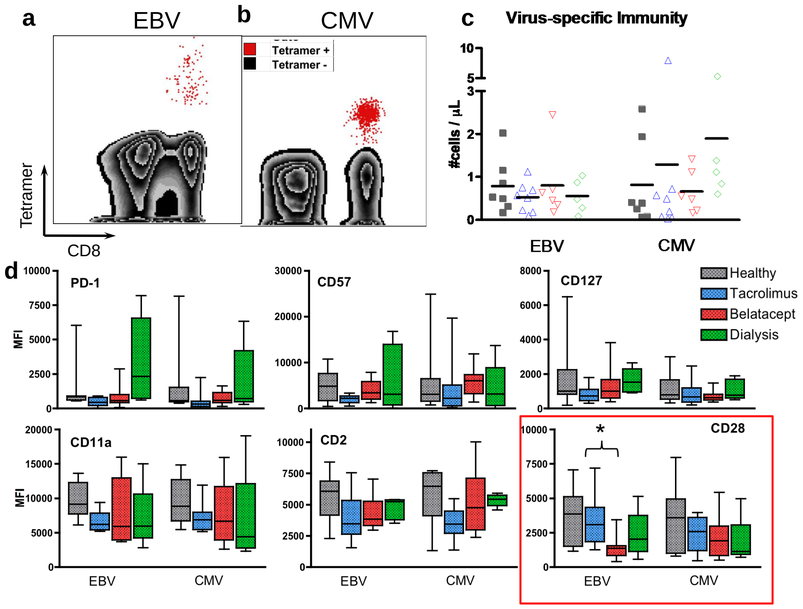

Figure 4. Belatacept treatment results in a population of EBV-specific T cells with decreased CD28 expression. Lymphocytes were stained with tetramers specific for EBV and CMV (a,b). There was no difference in the absolute number of viral-specific cells between groups (c), or in the expression of most activation markers. However, EBV-specific T cells did demonstrate decreased expression of CD28 (d, bottom panel, red box).

Conclusions

1. Long-term therapy with belatacept results in a population of T cells with decreased expression of the costimulatory molecule CD28.
1. Belatacept-treated subjects maintain some markers of T cell functional capacity despite a more senescent phenotype than subjects receiving conventional therapy with tacrolimus.
1. Virus-specific immune phenotype in belatacept-treated subjects remains largely unchanged compared to patients treated with conventional therapy; however CD28 expression is decreased on EBV-specific T cells in belatacept-treated subjects.
1. This cross-sectional study reveals patterns of immune alteration which should be monitored in future longitudinal studies.

References:

Vincenti F et al. A Phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). Am J Transplant 2010; 10(3):535-46.

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