Evidence for Immune Activation in Kidney Transplant Recipients Who develop De Novo Anti-HLA Antibodies After Transplantation: Interim Report of CTOT-02

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Background

CTOT-02 is a 2-stage prospective, multi-center, double-blind, randomized, controlled trial :

Stage I: Screening Study

Unsensitized kidney transplant recipients, 3 to 36 months post-transplant, are screened every 3 months (up to 36 months post-transplant) for development of *de novo* anti-HLA antibodies by Luminex technology®.

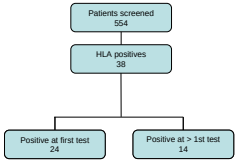
Stage II: Randomized Trial

Anti-HLA Ab confirmed positive subjects undergo a baseline measured GFR and biopsy to determine eligibility for randomization. Eligible subjects are then randomized (1:1) to receive rituximab* or placebo.

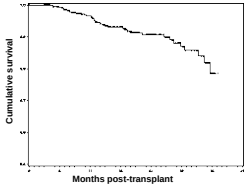
Methods

Cytokine levels measured every 3 months. All subjects with *de novo* Ab ('positives') and 129 randomly selected subjects without *de novo* Ab ('negatives') were selected for interim analysis. Data were examined by group (positives vs negatives) and serially. Statistical analyses were performed using t-test, Chi Square or Fisher's exact test for clinical data and Mann-Whitney U test and logistic regression model for cytokines.

CTOT-02 screening phase



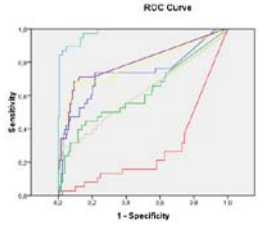
Conversion-free survival



Results

Clinical Results

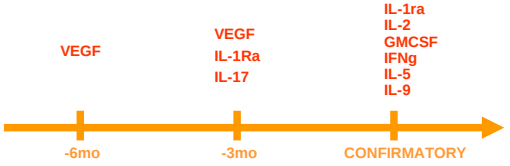
	HLA Ab positives n = 38	HLA Ab negatives n = 129	p-value
Age (y)	47.3	47.8	NS
Time post-transplant (mo)	12.0	14.0	NS
HLA A-B-DR mismatch (n)	3.2	3.7	NS
Initial PRA (%)	2.7	1.1	NS
Initial SCr (mg/dl)	1.4	1.5	NS
DGF (%)	18.4	12.9	NS
Final SCr (mg/dl)	1.3	1.4	NS
Infection (%)	15.7	10.8	NS
Gender (% male)	47.4	72.1	0.005
Donor – deceased (%)	34.2	45.2	0.232
Time on study (mo)	3.8	5.7	0.036
Rejection (%)	21.0	2.3	< 0.001
Donor – living related (%)	47.4	25.8	0.032
Donor – living unrelated (%)	18.4	29.0	



Immunosuppressive Medication

	HLA Ab positives n = 38	HLA Ab negatives n = 129	p-value
Prednisone (%)	50.0	57.4	NS
CNI (%)	93.8	97.0	NS
MMF (%)	87.5	85.1	NS
Sirolimus (%)	21.9	11.9	NS
Thymoglobulin (%)	47.4	48.8	NS
IL2-RI (%)	23.7	28.0	NS
Alemtuzumab (%)	26.3	11.6	0.037

Predictive value of cytokines & Anti HLA Ab response 32



Cytokine Results (pg/ml)

	HLA Ab positives	HLA Ab negatives	p-Value
IFNγ	12.9	2.6	< 0.001
IL12(p70)	3.4	1.0	< 0.001
IL-13	1.4	1.0	< 0.001
IL-4	22.2	1.0	< 0.001
IL-5	3.6	1.0	< 0.001
IL-6	13.4	5.2	< 0.001
IL-7	39.2	4.7	< 0.001
IL-9	90.5	1.0	< 0.001
TNFα	13.6	4.7	< 0.001
GMCSF	1.0	7.3	< 0.001

	HLA Ab positives	HLA Ab negatives	p-Value
MCP-1	455.0	566.0	0.003
IL-15	5.7	2.9	0.006
IL-17	2.2	1.0	0.006
IL-2	1.0	1.0	0.009
IL-1Ra	27.8	11.8	0.025
IL-1β	1.3	1.0	0.041
IL12(p40)	2.7	1.0	0.051
VEGF	241.0	112.0	0.060
IP-10	257.7	209	0.162
IL-10	6.5	3.5	0.181
IL-8	19.6	11.2	0.976

Conclusions

Rate of conversion from anti HLA negative to anti HLA positive is around 20% at 36 months post transplant. Female sex, living donors and rejection rate higher in anti-HLA Ab positive group. Use of Alemtuzumab as induction therapy is associated with higher Ab conversion rate. Antibody positive subjects have a different circulating cytokine profile from Ab negative subjects. Preliminary results suggest that changes in the circulating cytokine profile predict the development of anti-HLA antibodies

** Study drug (rituximab and placebo) provided by Genentech Inc. and Biogen Idec. This research was performed as a project of the Clinical Trials in Organ Transplantation, a collaborative clinical research project headquartered at the National Institute of Allergy and Infectious Diseases.*