Immune Tolerance Network

Abstracts

at the

2009 American Transplant Congress

Boston, MA

May 30 – June 3, 2009

www.immunetolerance.org

Monday, June 1, 2009 8:45 AM

Plenary Session II (8:30 AM-10:00 AM)

[189] ITN029ST: Immunosuppression Withdrawal in Pediatric Recipients of Parental Living Donor Liver Transplants: Preliminary Results of a Pilot Study.

S. Feng, U. Ekong, S. Lobritto, A. Demetris, P. Rosenthal, E. Alonso, N. Tchao Surgery, UCSF, San Francisco, CA; Pediatrics, Northwestern U, Chicago, IL; Pediatrics, Columbia U, New York, NY; Pathology, U Pittsburgh, Pittsburgh, PA; UCSF/ITN, San Francisco, CA

Background: Lifelong immunosuppression (IS) confers morbidity and mortality for pediatric liver transplant (tx) recipients. ITN029ST is a prospective, multicenter, single arm pilot trial of complete IS withdrawal for pediatric recipients of parental liver grafts.

Methods: From 5/06 to 7/08, 20 recipients were enrolled at 3 centers. Inclusion criteria included 1) tx with a parental graft as a child >4 yrs prior to enrollment for diseases other than viral or autoimmune hepatitis, 2) stable graft function on calcineurin inhibitor monotherapy, and 3) screening liver biopsy showing no rejection and fibrosis stage <2 (Ishak). IS was withdrawn according to protocol over >8 months. Tapering was terminated for any delay in dose reduction >4 wks or any episode of rejection requiring treatment. Planned follow-up after successful IS withdrawal is for 4 yrs and includes protocol biopsies; safety follow-up after failed IS withdrawal is for 1 yr.

Results: For the 20 enrollees, median (range) age at tx was .58 (.3-7.5) yrs and at enrollment was 8.5 (5-15) yrs. Eleven participants successfully weaned IS over 8.2 (8-12) mos. They have been off IS for 14.9 (3-20) mos with normal graft function and without rejection since IS discontinuation. Tapering was terminated in 4 patients: 1 for inclusion criteria violation, 1 for moderate acute rejection treated with corticosteroids, and 2 for abnormal liver tests with biopsies non-diagnostic of rejection. 5 patients are still tapering. Autoantibody and alloantibody titers have not increased with IS weaning.

Conclusion: Preliminary results suggest that IS withdrawal is safe in selected pediatric liver tx recipients. Substantial efforts are underway to identify molecular signatures predictive of operational tolerance. Our findings justify larger studies to better define the safety, efficacy, benefit, and generalizability of IS withdrawal for the pediatric liver tx population.

ITN029ST: Participant Demographics and Immunosuppression Withdrawal Status

ID	Age at Tx (y)	Sex	Liver Disease	Age at Enrollment (y)	CNI	Start CNI Dose (mg)	Status	Last CNI Dose Date
1	.32	M	BA	8.23	Tac	1 bid	Off IS	3/6/07
2	.57	M	BA	9.14	Tac	.35 bid	Off IS	2/27/07
3	.55	F	BA	8.75	Tac	.25 bid	Off IS	3/20/07
4	.60	M	BA	12.14	Tac	.50 bid	Off IS	7/24/07
5	.39	M	BA	10.24	CyA	45 bid	Off IS	12/25/07
6	.76	F	BA	6.96	Tac	1 bid	Failed	
7	.40	F	BA	11.75	CyA	38 bid	Off IS	7/1/08
8	7.48	F	OTC Def	15.27	Tac	4.5 bid	Failed	
9	.76	M	BA	5.22	Tac	.50 bid	Tapering	
10	.44	F	BA	6.68	CyA	25 bid	Tapering	
11	.62	M	BA	6.60	CyA	50 bid	Off IS	8/23/07
12	.55	F	BA	11.18	CyA	50 qd	Off IS	5/5/07
13	.70	F	BA	13.42	Tac	1 od	Terminated	
14	.32	F	a1AT Def	10.29	CyA	35 qd	Off IS	7/6/07
15	1.07	M	BA	6.23	Tac	1am /.5@ pm	Failed	
16	2.43	M	Byler's	8.82	Tac	2 od	Off IS	12/23/07
17	1.45	M	NSC	7.04	Tac	1 od	Off IS	7/31/08
18	.47	F	BA	6.05	Tac	1 od	Tapering	
19	.47	M	BA	5.27	Tac	.32 bid	Tapering	
20	.64	M	BA	6.03	CyA	50 bid	Tapering	

Tuesday, June 2, 2009 5:30 PM

Poster Session: Late-Breaking Posters Abstracts (5:30 PM-6:30 PM)

[LB08] Peripheral B Cell Markers Identify Tolerant Renal Transplant Recipients.

Kenneth A. Newell, Adam Asare, Allan D. Kirk, Trang Gisler, Manikkam Suthanthiran, William J. Burlingham, Katarzyna Bourcier, William H. Marks, Laurence A. Turka, Vicki Seyfert-Margolis Department of Surgery, Emory University, Atlanta, GA; Immune Tolerance Network, UCSF, San Francisco, CA; Department of Medicine, Cornell University, New York, NY; Department of Surgery, University of Wisconsin, Madison, WI; Organ Transplant Program, Swedish Medical Center, Seattle, WA; Department of Medicine, University of Pennsylvania, Philadelphia, PA

Introduction. Biomarkers predictive of tolerance are key tools for protocols studying immunosuppression minimization/discontinuation. We report on the identification tolerance markers in renal transplant recipients.
Methods. An initial cohort of tolerant kidney transplant recipients (TOL, off all IS for > 1yr with stable function, N=19) were compared to recipients with stable function on standard immunosuppression (SI, N=24), and healthy controls (HC, N=18). A separate cohort of TOL (n=6) SI (n=6) HC (n=24) were recruited as an independent test set for biomarker testing. Initial biomarkers were defined using microarrays on peripheral blood RNA, flow cytometry on whole blood and PCR of urine lymphocytes. Independent verification of these markers was performed using multi-plex real time PCR on all subjects (initial and test set), and flow cytometry on the second test set of participants. Finally, extensive B cell subset analysis was performed on frozen PBMC's from all participants.
Results. We initially defined that tolerant participants exhibited a novel signature of increased B cells in the peripheral blood, as well as increases in B cell development genes. Multi-plex real time PCR analyses of initial and test set samples from the TOL and SI identified 3 transcripts, all corresponding to immunoglobulin variable region genes, that distinguish TOL from SI patients, with 100% accuracy for TOL and 83% accuracy for SI on the test set samples. Independent verification of the initial flow cytometry B cell signature was obtained using samples from the test set described above. B cell subtyping identified increased navie Bcell numbers in the TOL vs. the SI and HC groups.
Conclusions. These data suggest that an increases in B cell numbers and in the genes they express may identify tolerant renal transplant recipients. The powerful predictive value of a very small number of genes makes this approach clinically feasible and may facilitate rational design of tolerance-inducing regimens.

Monday, June 1, 2009 5:30 PM

Poster Session: Strategies in Immune Monitoring (5:30 PM-6:30 PM)

[1561] Validated Biomarkers of Immune Tolerance in Renal Transplants.

M. Hernandez-Fuentes, E. Perucha, P. Sagoo, B. Sawitzki, S. Tomiuk, D. A. Stephens, P. Miqueu, S. Chapman, L. Craciun, S. Brouard, M. Giral, V. Seyfert-Margolis, K. Newell, L. Turka, M. Goldman, K. Wood, A. Warrens, H. D. Volk, J. P. Soulillou, U. Janssen, R. I. Lechler, www.transplant-tolerance.org.uk/ParticipantPhysicians.aspx King's College London, London, United Kingdom; Charité University Medicine, Berlin, Germany; ITERT-INSERM U643, Nantes, France; University of Oxford, Oxford, United Kingdom; McGill University, Montreal, QC, Canada; Universite Libre Bruxelles, Brussels, Belgium; Miltenyi Biotec GmbH, Bergisch Gladbach, Germany; Imperial College London, London, United Kingdom; Immune Tolerance Network

To identify renal transplant recipients in whom immunosuppressive drugs can safely be reduced or even, ultimately, withdrawn, it is essential to define a set of biomarkers of transplant tolerance. We have concluded a multi-centre study aimed at identifying a "signature" of clinical transplant tolerance. Samples from five groups of renal transplant recipients: drug-free tolerant patients that were functionally stable despite remaining immunosuppression-free > 1 year (n=11); stable patients on minimal immunosuppression (n=11); stable patients maintained with calcineurin inhibitors (n=30); stable patients maintained on CNI-free immunosuppression regimen (n=12); and patients on chronic rejection (n=9).

Several biomarkers and bioassays, were combined to provide an immunological signature of the tolerant state.

When drug-free tolerant patients were compared to the rest we observed significant differences in percentages of peripheral blood B and NK lymphocytes, in the absence of anti-donor antibodies. Differential expression of several immune relevant genes in the drug-free group compared to the rest of the groups was observed using microarrays. TCR landscape analysis highlighted differences between the V repertoires of drug-free tolerant recipients and chronic rejection patients. Direct pathway donor-specific hyporesponsiveness by IFN ELISpot and lack of indirect pathway anti-donor responses assessed by trans-vivo DTH were observed in drug-free patients. These results have been validated in an independent cohort of patients that includes a different set of drug-free tolerant recipients in the USA (n=86).g

Conclusions: The diagnostic capabilities of the combined results of several of the above mentioned biomarkers and bioassays were excellent, with high specificity, sensitivity, and positive predictive value, with verification in an independent cohort.