Is It EVER Safe to Discontinue Immunosuppression after Pediatric Liver Transplantation?

Less or none?
Safe or Sorry?

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Washington DC
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Disclosures

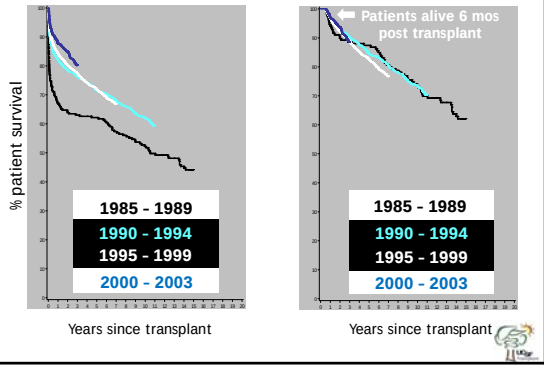
Clinical trial funding

- NIAID
- NIDDK
- ITN
- Novartis

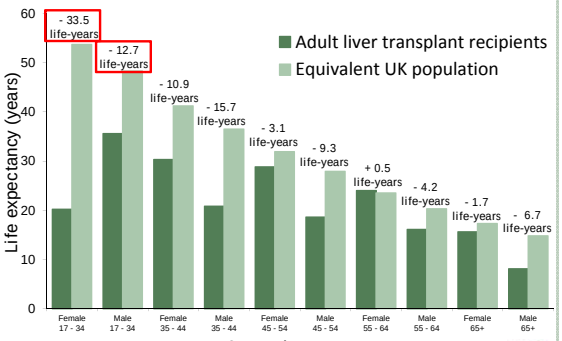
Consulting

- Novartis
- Quark

Early versus late outcomes after liver transplantation



SHORTENED LIFESPAN



THREATS TO RECIPIENT HEALTH

The Liver Meeting 2009 — BOSTON OCT 30 - NOV 3

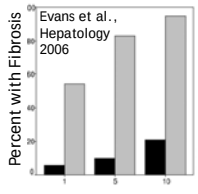
Long-Term Outcomes of Adult and Pediatric Liver Transplantation

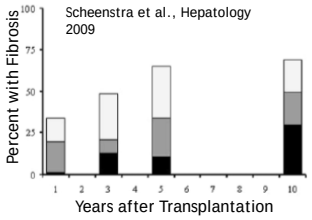
AASLD / ILTS Transplant Course

Course Directors: Sandy Feng, MD, PhD and Jan Lerut, MD, PhD

1:30 – 1:45pm	Chronic Kidney Disease Rajender Reddy, MD
1:45 – 2:00pm	Hypertension / Cardiovascular Risk Factors Olaf Guckelberger, MD
2:00 – 2:15pm	Diabetes Mellitus Georges-Philippe Pageaux, MD
2:15 – 2:30pm	Obesity / Hyperlipidemia / Metabolic Syndrome Michael R. Charlton, MD
2:30 – 2:45pm	De novo Malignancy J. Ignacio Herrero, MD

THREAT TO ALLOGRAFT HEALTH





Fibrosis	Interval from Transplantation to Biopsy <6 Years	≥6 Years	Total
<Stage 3	20	29	49
≥Stage 3	0	14	14
Total	20	43	63

NOTE: $P = 0.003$.

Ekong et al., Liver Transplant 2008

IMMUNOSUPPRESSION: A LIFELONG BURDEN?

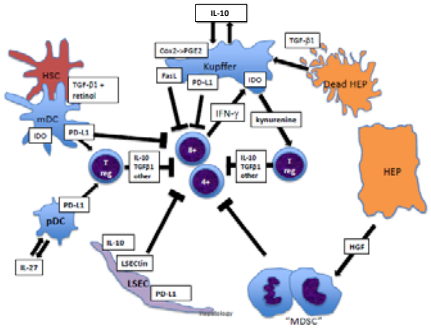
"Tolerogenic Effects of Porcine Liver Allografts"

RY Calne, RA Sells, JR Pena, DR Davis,
PR Millard, BM Herbertson, RM Binns, DR Davis.

Pigs given no immunosuppression survive long periods with liver allografts; rejection has been minimal whether the donor and recipient were closely related or of different breeds. In contrast, rejection of both skin and kidney allografts by the pig is usually complete within 2 weeks.

Brit J Surg, 1969, Vol. 56, No. 9

MULTIPLE MECHANISMS EXIST WITHIN THE LIVER TO BIAS AN IMMUNE RESPONSE TOWARDS TOLERANCE RATHER THAN ACTIVATION

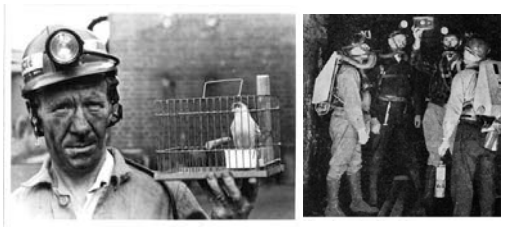


Crispe IN. Hepatology 2014

PHASE I PILOT TRIAL

WISP-R: Immunosuppression Withdrawal for Pediatric Parental Living Donor Liver Transplant Recipients

Learning from the Canaries in the Coalmines



WISP-R: Immunosuppression Withdrawal for Stable Pediatric Liver Transplant Recipients

WISP-R: Immunosuppression Withdrawal for Pediatric Parental Living Donor Liver Transplant Recipients

Single arm, three center pilot trial of 20 patients

UCSF Children's Hospital

Sandy Feng, M.D., Ph.D.
Phil Rosenthal, M.D.
John Roberts, M.D.

Children's Memorial Hospital Where kids come first

Udeme Ekong, M.D., Ph.D.
Estella Alonso, M.D.
Peter Whitington, M.D.

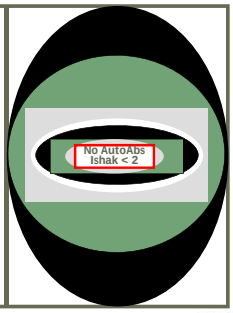
Morgan Stanley Children's Hospital of NewYork-Presbyterian

Steven Lobritto, M.D.
Jean Emond, M.D.

Feng et al., JAMA 2012

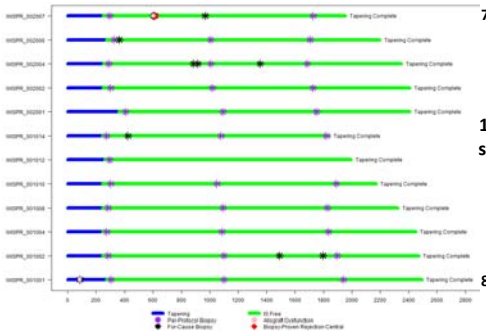
WISP-R Inclusion / Exclusion Criteria

Deceased Donor



Feng S et al., JAMA 2012

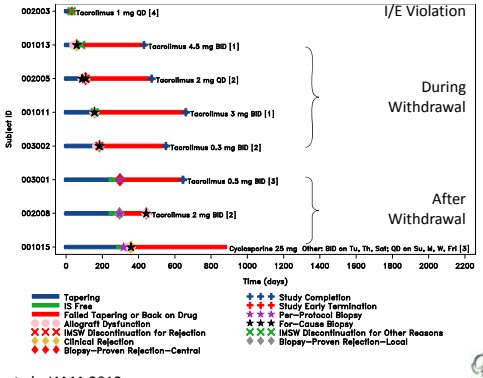
WISP-R: 12 of 20 Were Operationally Tolerant



Feng S et al., JAMA 2012

As of 10/1/15

WISP-R: 8 of 20 Participants Were Not Tolerant



Feng et al., JAMA 2012

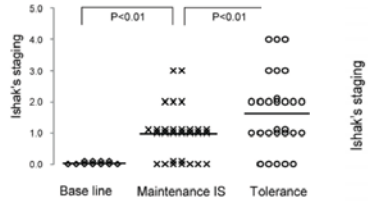
Increased Time after Transplantation and Absence of Inflammation at Baseline were Associated with Operational Tolerance

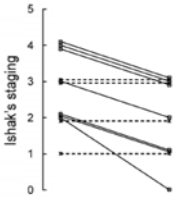
Characteristic		Tolerant n = 12	Non-Tolerant n = 7	P value
Age (years)	At Transplant	0.57 (0.32 - 2.43)	0.64 (0.44 - 7.48)	0.41
	At Study Entry	8.98 (5.22 -12.14)	6.55 (5.03 - 15.27)	0.24
Male Gender		8 (66.7%)	3 (42.9%)	0.38
Interval Between Transplant and Study Entry (years)		***100.6 (53.5 - 138.7)***	***73.0 (52.7 - 93.5)***	***0.02***
CNI at entry	Cyclosporine	5 (41.7)	2 (28.6)	.66
	Tacrolimus	7 (58.3)	5 (71.4)	
History of Rejection		7 (58.3%)	4 (57.1%)	> 0.99
Baseline ALT (U/mL)		31 (18 - 48)	30 (22 - 38)	0.85
Baseline GGT (U/mL)		27 (12 – 88)	16.0 (10 – 69)	0.82
Baseline Biopsy: Absence of Inflammation		***11 (91.7%)***	***3 (42.9%)***	***0.04***

Long-Term Follow-up of Spontaneously Tolerant Children

Is the allograft healthy?

Children on no IS have higher fibrosis stage than children on maintenance IS

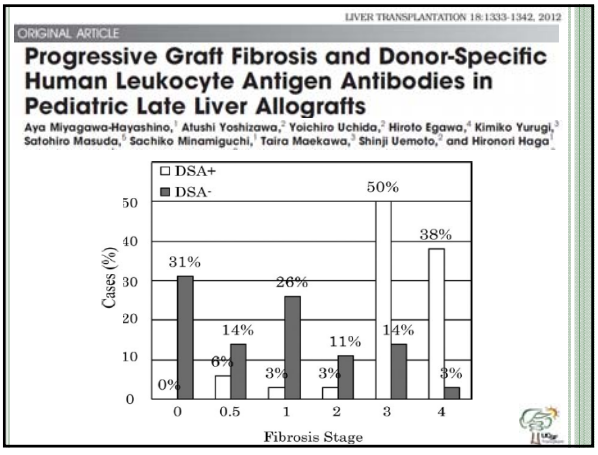




Variable	TOL	NON-TOL	P Value
Recipient age at tx	1.0 ± 1.7	4.2 ± 4.5	<0.01
Time between tx and bx	121 ± 42.8	52.2 ± 22.4	<0.01
Donor age + time between tx and bx	43.4 ± 6.0	38.6 ± 6.8	<0.01

- IS reintroduced in 11 pts for progressive/bridging fibrosis
- Interval 4 – 54 months (mean 14 months)

Yoshitomi et al., Transplantation 2009


LIVER TRANSPLANTATION 18:1333-1342, 2012

ORIGINAL ARTICLE

Progressive Graft Fibrosis and Donor-Specific Human Leukocyte Antigen Antibodies in Pediatric Late Liver Allografts

Aya Miyagawa-Hayashino,[1] Atushi Yoshizawa,[2] Yoichiro Uchida,[2] Hiroto Egawa,[4] Kimiko Yurugi,[3] Satohiro Masuda,[1] Sachiko Minamiguchi,[1] Taira Maekawa,[3] Shinji Uemoto,[2] and Hironori Haga[1]

Original Clinical Science

Donor-Specific HLA Antibodies Are Associated With Late Allograft Dysfunction After Pediatric Liver Transplantation

Laura J. Wozniak, MD, MS,[1] Michelle J. Hickey, PhD,[2,3] Robert S. Venick, MD, MS,[1,4] Jorge H. Vargas, MD,[1] Douglas G. Farmer, MD,[4] Ronald W. Busuttil, MD, PhD,[4] Sue V. McDiarmid, MD,[1,4] and Elaine F. Reed, PhD[2,3]

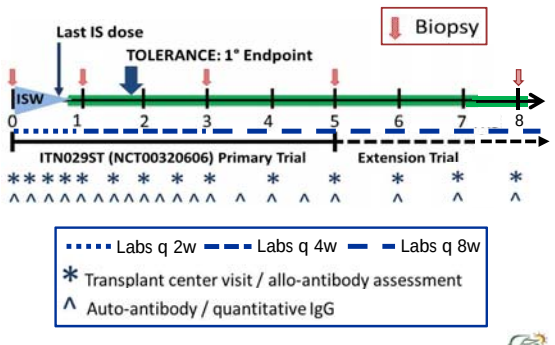
Associations between type of DSA and nontolerance

Type of DSA	Odds ratio (95% CI)	P
Any DSA	2.3 (0.7-7.5)	0.175
DSA with MFI > 13000	2.4 (0.7-8.2)	0.161
DQ DSA	5.6 (1.6-19.9)	0.006
C1q-binding DSA	4.3 (1.1-16.4)	0.028

Multivariate predictors associated with DAIH and late ACR

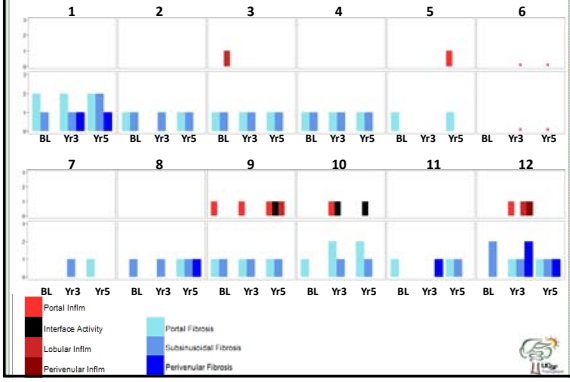
	Predictors of DAIH		Predictors of late ACR	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Age at transplant, y	1.2 (1-1.4)	0.038	1.3 (1.1-1.6)	0.005
Positive DQ DSA	12.5 (2.3-69)	0.004	10.8 (2-59.3)	0.006

FOLLOW-UP STRATEGY TO ENSURE SAFETY

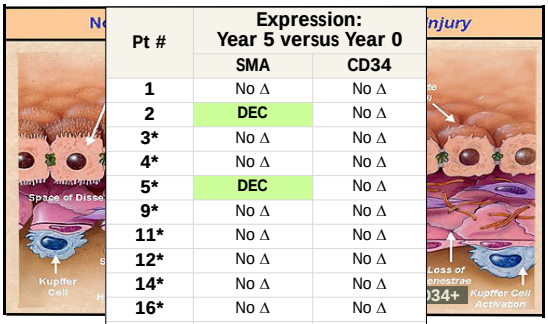


Feng S et al., JAMA 2012

LONG-TERM FOLLOW-UP OF TOLERANT SUBJECTS: INFLAMMATION AND FIBROSIS BY COMPARTMENT



No increase in smooth muscle actin or CD34 expression



Pt #	Expression: Year 5 versus Year 0	
	SMA	CD34
1	No Δ	No Δ
2	DEC	No Δ
3*	No Δ	No Δ
4*	No Δ	No Δ
5*	DEC	No Δ
9*	No Δ	No Δ
11*	No Δ	No Δ
12*	No Δ	No Δ
14*	No Δ	No Δ
16*	No Δ	No Δ
17	No Δ	No Δ

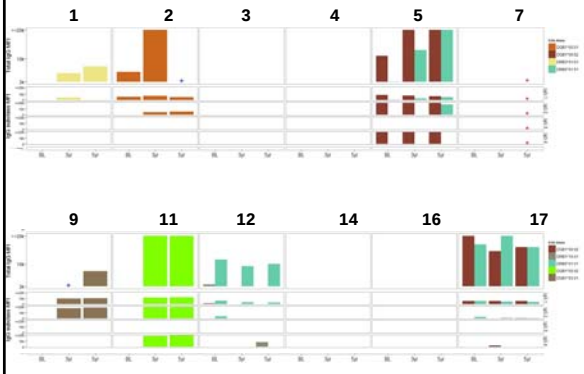
Medscape (htt

Class II DSA profiles prior to, during and after immunosuppression withdrawal

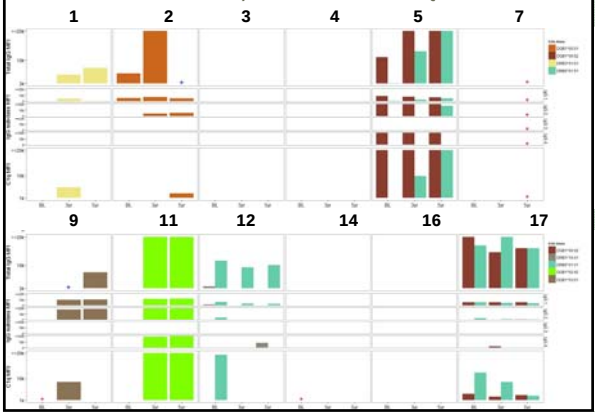
Pt ID	Baseline	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5
1	No Class II DSA	No Class II DSA	No Class II DSA	DRB3*0101 5,000	DRB3*0101 12,000	DRB3*0101 7,300
4		DQB1*03:02 2,300	No Class II DSA	No Class II DSA	No Class II DSA	No Class II DSA
9		DQB1*03:01 9,000	DQB1*03:01 4,400	No Class II DSA	DQB1*03:01 3,800	DQB1*03:01 7,400
11		DQB1*0202 16,000	DQB1*0202 17,000	DQB1*0202 >20,000	DQB1*0202 >20,000	DQB1*0202 >20,000
16		DRB1*15:01 4,000	No Class II DSA	No Class II DSA	No Class II DSA	No Class II DSA

Pt ID	Class II DSA	Baseline	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5
2	DQB1*0501	5,400	16,000	2,000	>20,000	>20,000	Not detected
5	DQB1*0602	11,000	>20,000	19,000	>20,000	13,000	>20,000
	DRB5*0101	2,000	5,000	8,000	13,000	13,000	>20,000
12	DRB1*1501	2,600	5,000	2,200	Not detected	3,300	Not detected
	DRB5*0101	11,500	18,000	9,300	9,200	14,000	10,000
17	DQB1*0602	>20,000	11,000	14,000	14,500	15,000	16,000
	DRB5*0101	17,000	17,500	>20,000	>20,000	>20,000	16,000

Class II DSA single antigen and IgG subclass MFIs



Class II DSA single antigen, IgG subclass and C1q binding MFIs



Immunosuppression Withdrawal for Stable Pediatric Liver Transplant Recipients

iWITH

NIAID NIDDK Immune Tolerance Network

Stable allograft histology in spite of . . . a persistent/active allo-immune response

- The humoral response of these operationally tolerant pediatric liver transplant recipients *generally* mirrors that reported for kidney and heart recipients
  - Class II DSA / α-DQ specificity
  - High MFI DSA
  - DSA with complement binding capability
  - ***Absence of IgG3 DSA / presence of IgG 2 / 4 DSA***
- However, unlike kidney and heart allografts, liver allografts did not exhibit progressive histopathology
  - Liver, compared to heart and kidney, has lower baseline Class II expression on the microvascular endothelium
  - Liver has inherent bias towards immune tolerance

THE HORIZON

- Can we identify a biomarker of operational tolerance?
  - Test subjects who are earlier after transplantation
- What are the mechanism(s) of tolerance?
- Can we accelerate or induce tolerance?
  - Clinical trials utilizing autologous, ex vivo expanded, donor-reactive regulatory T cells