June 12, 2016
1:00 PM – 2:15 PM
Sheraton Boston Hotel
Republic Ballroom

A Balancing Act:

Immunosuppression in Transplant Medicine

Supported by an educational grant from Novartis Pharmaceuticals Corporation

Provided by
CME Outfitters

Faculty

- **Flavio G. Vincenti, MD**
  Professor of Clinical Medicine and Surgery
  Departments of Medicine and Surgery
  University of California San Francisco
  San Francisco, CA
- **Lewis W. Teperman, MD, FACS**
  Vice Chairman of Surgery
  Director of Transplantation
  Director, Northwell Health System Transplant Center
  Manhasset, NY
  Professor, Hofstra University Medical School
  Hempstead, NY

Flavio G. Vincenti, MD

Disclosures

- ***Research Support:*** Alexion; Bristol-Myers Squibb Company; Genentech, Inc.; Immucor; Novartis Pharmaceuticals Corporation

Lewis W. Teperman, MD

Disclosures

- Dr. Teperman has no disclosures to report

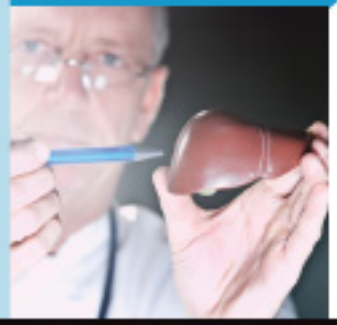
Learning Objectives

- Describe the causes of antibody-mediated complications in kidney and liver transplants.
- Implement regular monitoring strategies that can optimize appropriate immunosuppression while managing side effects in transplant patients.
- Engage transplant patients to become participants in their treatment to promote adherence to medications and improve outcomes.

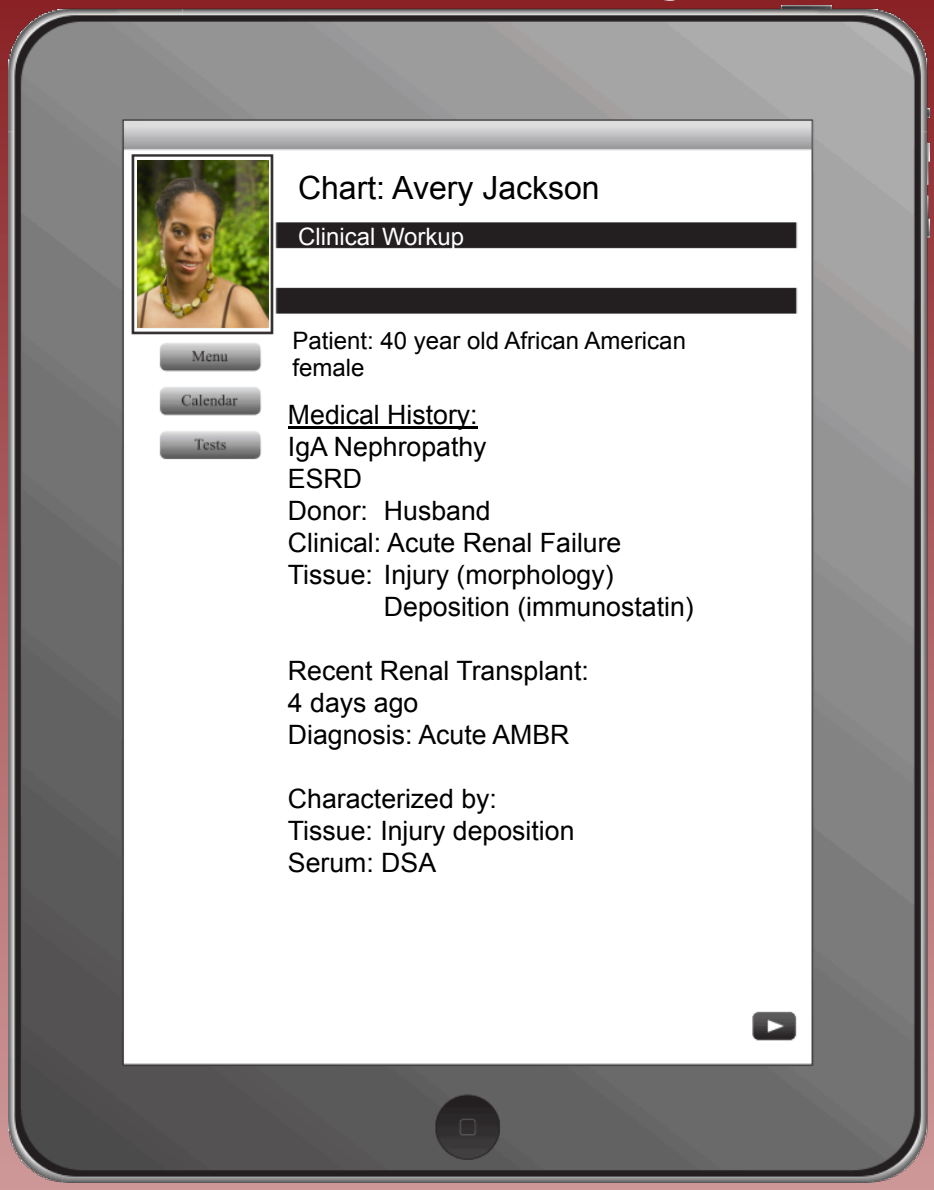
Agenda

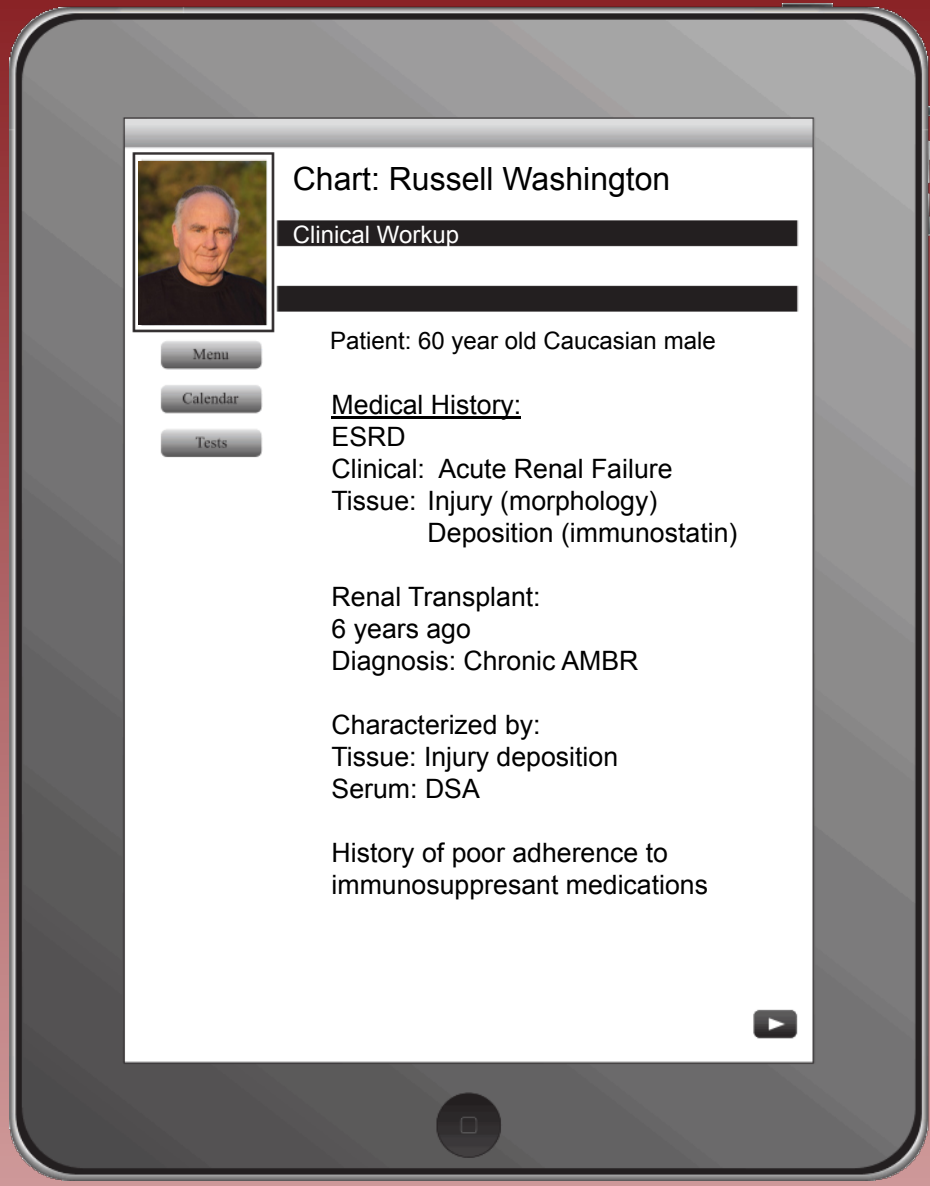
1:15 – 1:20 PM	Introductions
1:20 – 1:30 PM	The Causes of Allograft Failure
1:30 – 1:45 PM	Balancing Immunosuppression Levels to Optimize Care
1:45 – 1:55 PM	Engaging Patients to Improve Adherence and Care
1:55 – 2:05 PM	Applying Novel Technology To Transplant Medicine
2:05 – 2:15 PM	Q&A/Conclusions

The Challenges of Antibody-Mediated Rejection



Two Patients with Antibody Mediated Rejection





Audience Response

Which of these patients has a better prognosis for allograft survival?

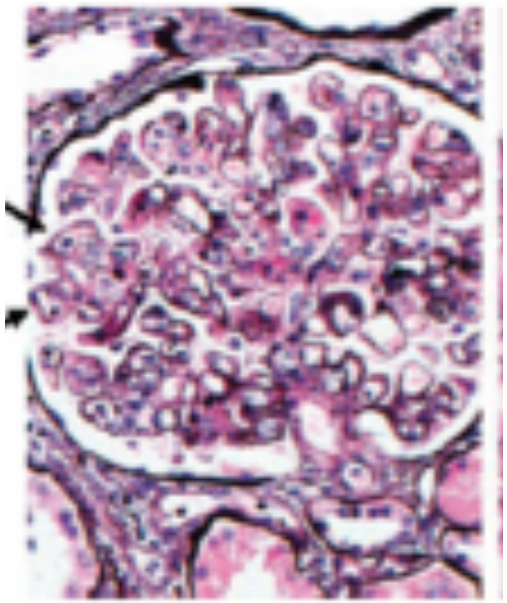
A. Avery (acute AMR)
B. Russell (chronic AMR)
C. Both patients
D. Neither patient

Early vs. Late AMR In Renal Transplant Recipients

	Early AMR	Late AMR (Chronic AMR)
Main risk factor	Positive panel reactivity antibody before transplantation, including factors causing sensitization	Withdrawal or reduction of immunosuppressants. Noncompliance with immunosuppressive therapy, young age
Antibody	Mostly pre-existing donor-specific antibodies	Mostly de novo donor-specific antibodies, especially HLA class-II antibodies
Clinical features	Very rapid graft dysfunction, significantly decreased urine output, and rapid graft dysfunction	Proteinuria, hypertension, progressive functional deterioration, and overt graft failure
Histology	ATN-like minimal inflammation; capillary and or glomerular inflammation and/or thrombosis; arterial—v3	May have chronic tissue injury, such as glomerular double contours, peritubular capillary basement membrane multilayering, interstitial fibrosis/tubular atrophy, and/or fibrous intimal thickening in arteries
Outcome	Treatment available but prognosis affected	Not reversible by treatment

Sun Q, Yang Y. *Clin Dev Immunol*. 2013;2013:859761.

Transplant Glomerulopathy (Late AMR)



Duplicated GBM

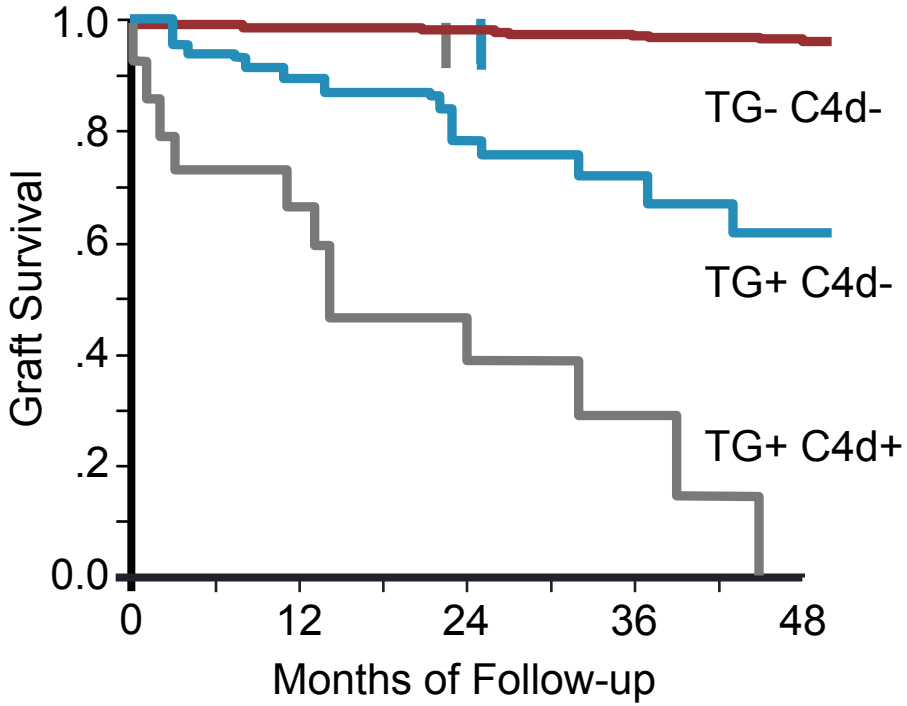
- Incidence
- 4% of protocol biopsies at 1 year
- Up to 20% at 5 years
- 22% of patients with DSA
- 45% of patients with acute AMR

Cosio FG, et al. *Am J Transplant*. 2008;8(3):492-496.

Transplant Glomerulopathy is Strongly Associated With Graft Loss

Multivariate Cox analysis of factors related to the development of TG

	Multivariate analysis	
Variables	**HR (CI)**	***P***
Acute antibody-mediated rejection	5.093 (2.77-9.37)	<.0001
Anti-HLA-II NV	1.860 (1.36-2.54)	<.0001
Anti-HLA-II DSA	3.195 (1.43-7.15)	.005
HLA mismatches		.437
Transplant number		.292



DSA = donor-specific activity; GFR = glomerular filtration rate; HR = hazard ratio; NV = normalized value; TG = transplant glomerulopathy.

Reprinted with permission from Issa N, et al. *Transplantation*. 2008;86(5):681-685.

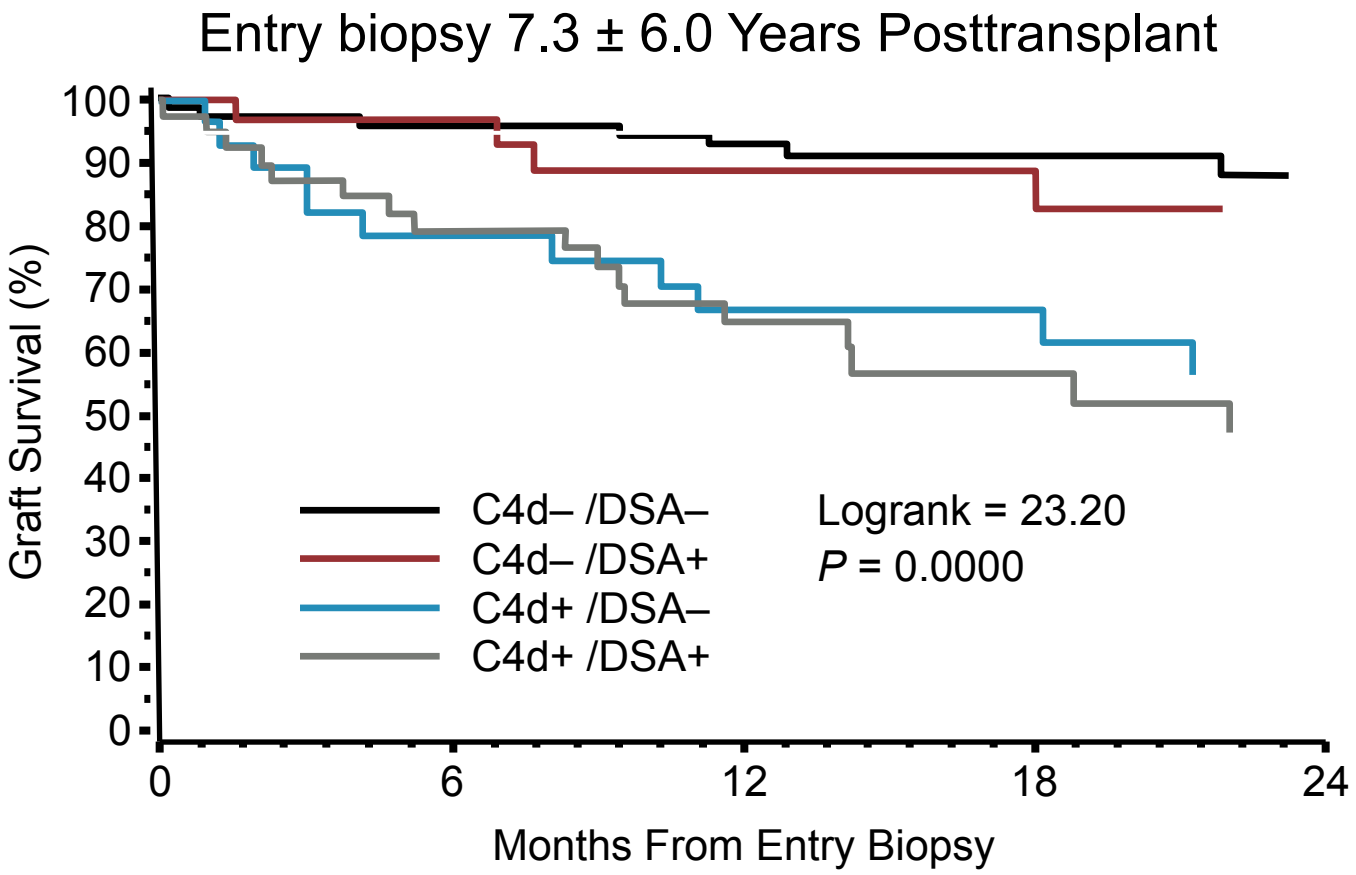
Schinstock CA, et al. *Curr Opin Nephrol Hypertens*. 2014;23(6):611-618.

Evidence for Antibody-Mediated Injury as a Major Determinant of Late Kidney Allograft Failure

- 173 subjects transplanted before October 1, 2005 (mean time after transplant) 7.3 ± 6.0 years) had a baseline serum creatinine level of 1.4 ± 0.3 mg/dL before January 1, 2006 and underwent biopsy for new onset graft dysfunction after that date (mean creatinine at biopsy 2.7 ± 16 mg/dL)

Gaston RS, et al. *Transplantation*. 2010;90(1):68-74.

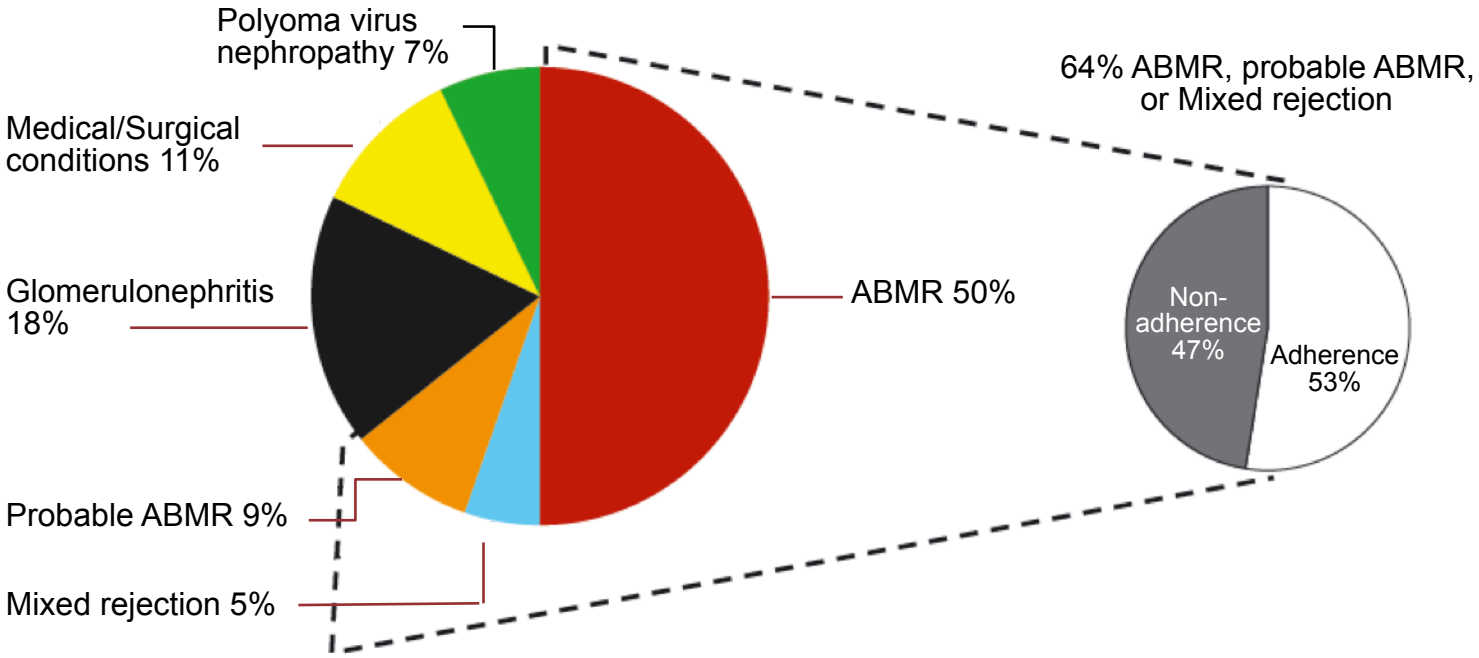
Antibody-Mediated Injury Compromises Long-Term Renal Allograft Survival: Results from the DeKAF Study



Reprinted with permission from Gaston RS, et al. *Transplantation*. 2010;90(1):68-74.

The Role of Antibody-Mediated Rejection and Nonadherence in Kidney Transplant

Distribution of Attributed Causes of Failure
Almost Half of Antibody-Mediated Rejection (ABMR) is Due to Nonadherence



N = 315

Sellarés J, et al. *Am J Transplant*. 2012;12(2):388-399.

Impact of Donor Specific Antibodies (DSA) on Outcome

- Patients with DSA have higher rates of antibody mediated rejection
- Patients with acute rejection who develop DSA have worse outcome
- Patients with antibody mediated rejection develop transplant glomerulopathy
- Patients who develop transplant glomerulopathy have worse outcome

What About AMR in Liver Transplants?

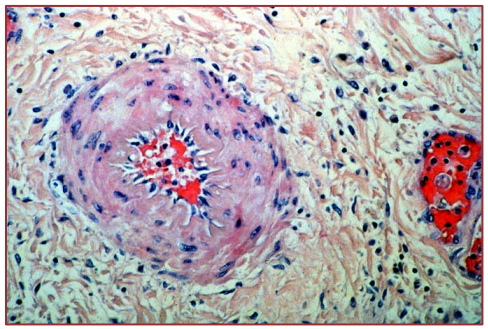
Evidence for Hyperacute Rejection of Human Liver Grafts: The Case of the Canary Kidneys

- Sequential liver and kidney transplantation from the same donor was performed in 2 patients
  - The kidney in Patient 1, which was transplanted after the liver, was hyperacutely rejected and removed 6 hours later
  - In Patient 2, who had a strongly positive cytotoxic cross-match with his donor, the liver suffered a massive but reversible injury, while the kidney never functioned
- The kidneys in these cases had served like the canaries which miners once used to detect a hostile environment.

Starzl TE, et al. *Clin Transplant*. 1989;3:37-45.

Antibody-Mediated Rejection of Human Orthotopic Liver Allografts

- 51 (24 primary) ABO-incompatible liver grafts were transplanted into 49 recipients
- There was a 46% graft failure rate during the first 30 days for primary ABO-I and 60% for non primary grafts, compared with an 11% graft failure rate for primary ABO compatible (ABO-C), cross-match negative matched patients
- Prominent arterial deposition of antibody and complement components was demonstrated by immunoflourescent staining. Elution studies confirmed the presence of tissue-bound, donor-specific isoagglutinins within the grafts.
- These studies confirm that antibody mediated rejection of the liver occurs



Demetris AJ, et al. *Am J Pathol*. 1988;132(3):489-502.

The Role of Donor-Specific HLA Alloantibodies in Liver Transplantation

- Presentation of acute AMR is otherwise unexplained liver allograft dysfunction
  - Falling platelet complement levels
  - Increased levels of circulating immune complexes
  - Persisted DSA of liver biopsy with microvascular injury in addition to other characteristics commonly associated with allograft rejections.

O'Leary JG, et al. *Am J Transplant*. 2014;14(4):779-787.

World Congress of Hepatology Working Group. *Hepatology.* 1995;22(2):648-54.

Proposed Diagnostic Criteria for Chronic Antibody-Mediated Rejection in Liver Allografts

- Paired serum, tissue, and data on 45 matched DSA-positive and DSA-negative recipients of a primary liver-only allograft from January 2000 to April 2009
- Blinded histopathologic evaluation demonstrated that DSA+ versus DSA- patients were more likely to have subtle inflammation and unique patterns of fibrosis, despite normal or near-normal liver function tests
- Propose chronic AMR: (1) DSA, and (2) elimination of other potential causes of a similar injury pattern

O'Leary JG, et al. *Am J Transplant*. 2016;16(2):603-614.

Role of Donor-Specific Antibodies (DSAs) in Antibody-Mediated Rejection

- Compared with the kidney, the liver appears to have resistance to AMR. The large size and unconventional sinusoidal microvascular bed of the liver may effectively reduce the relative endothelial damage from DSAs
- In addition, the secretion of high levels of soluble HLAs and their phagocytosis by sinusoidal Kupffer cells inactivates immune complexes
- Finally, the liver has a remarkable regenerative capacity following injury

Trotter JF. *Gastroenterol Hepatol (N Y)*. 2016;12(4):214-219.

Challenges In Defining The Roles Of DSAs and AMR in Liver Transplantation

- It occurs but it is a rare event: <1%
- Some experienced clinicians remain skeptical
  - As with any new concept, there is a general reluctance toward its acceptance
  - The majority of patients with DSAs have no evidence of graft dysfunction
  - The liver is inherently protected from this type of graft injury

Trotter JF. *Gastroenterol Hepatol (N Y)*. 2016;12(4):214-219.

Treatment of AMR in Liver Transplantation

- There is currently no agreed upon treatment once it occurs
  - Plasma exchange
  - Higher levels of immunosuppression
  - Hepatitis C treatment
  - Re-transplantation

Teperman L, et al. *Hepatology*. 1991;13(4):619-26.

Optimizing and Monitoring Immunosuppression

Is Therapeutic Drug Monitoring Enough to Insure Optimization of Drug Therapy?

- Many of the drugs currently used require therapeutic drug monitoring (TDM) to assure efficacy and safety.[1]
- With current treatment regimens, a relatively high proportion of transplant recipients experience underimmunosuppression or overimmunosuppression[2]
- Several promising biomarkers have been identified for determining patient alloreactivity, which help in assessing the risk of rejection and personal response to the drug; others correlate with graft dysfunction and clinical outcome.[2]

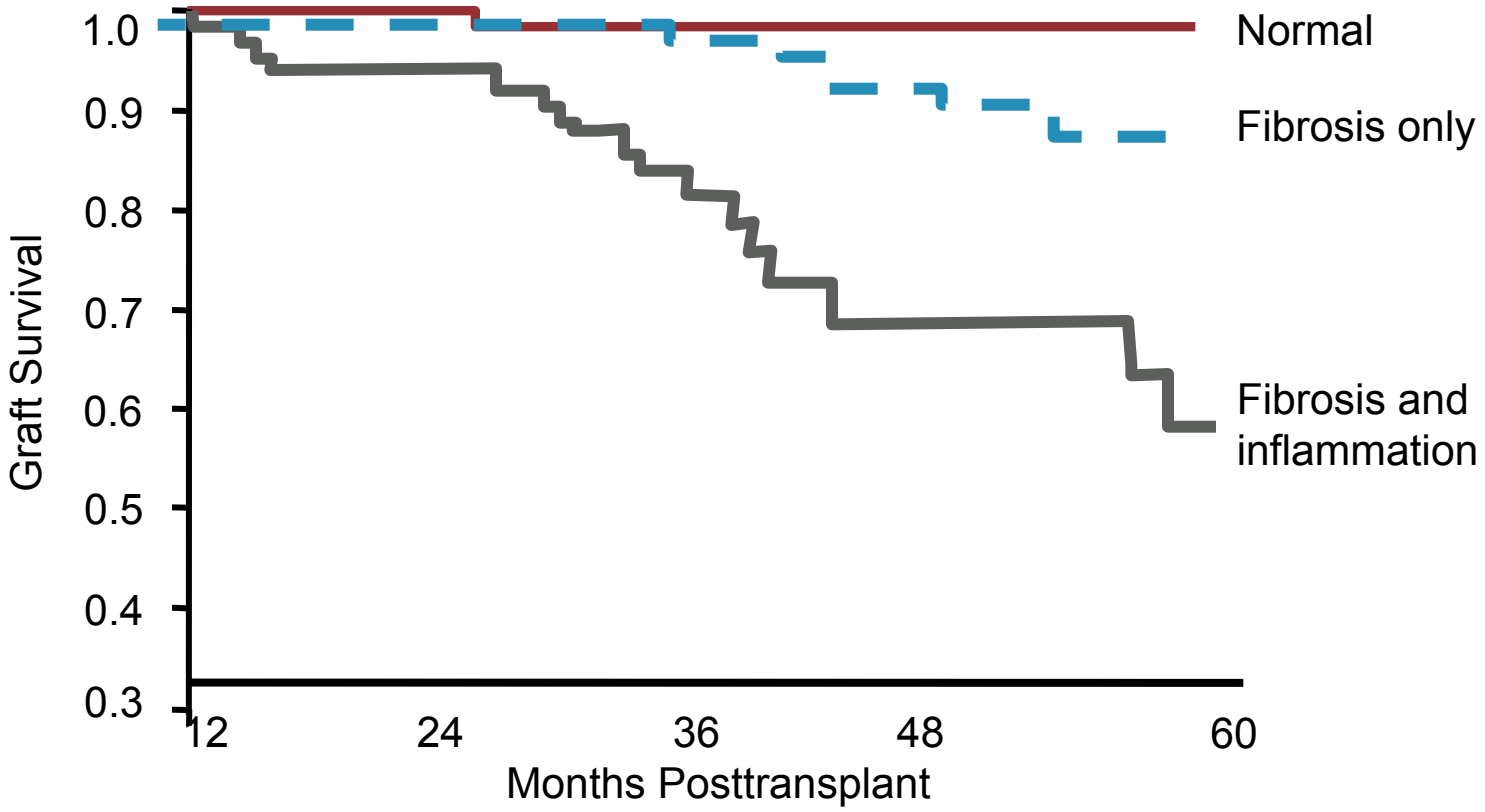
1.Christians U, et al. *Ther Drug Monit*. 2015;37(6):718-724.

2.Brunet M, et al. *Ther Drug Monit.* 2016r;38 Suppl 1:S1-S20

The Challenge of Optimizing Immunosuppression

- Maintaining efficacy
- Preventing DSA
- Preserving GFR

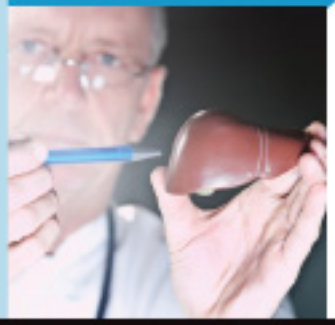
Inflammation Emerging as Another Important Marker of Late Allograft Dysfunction



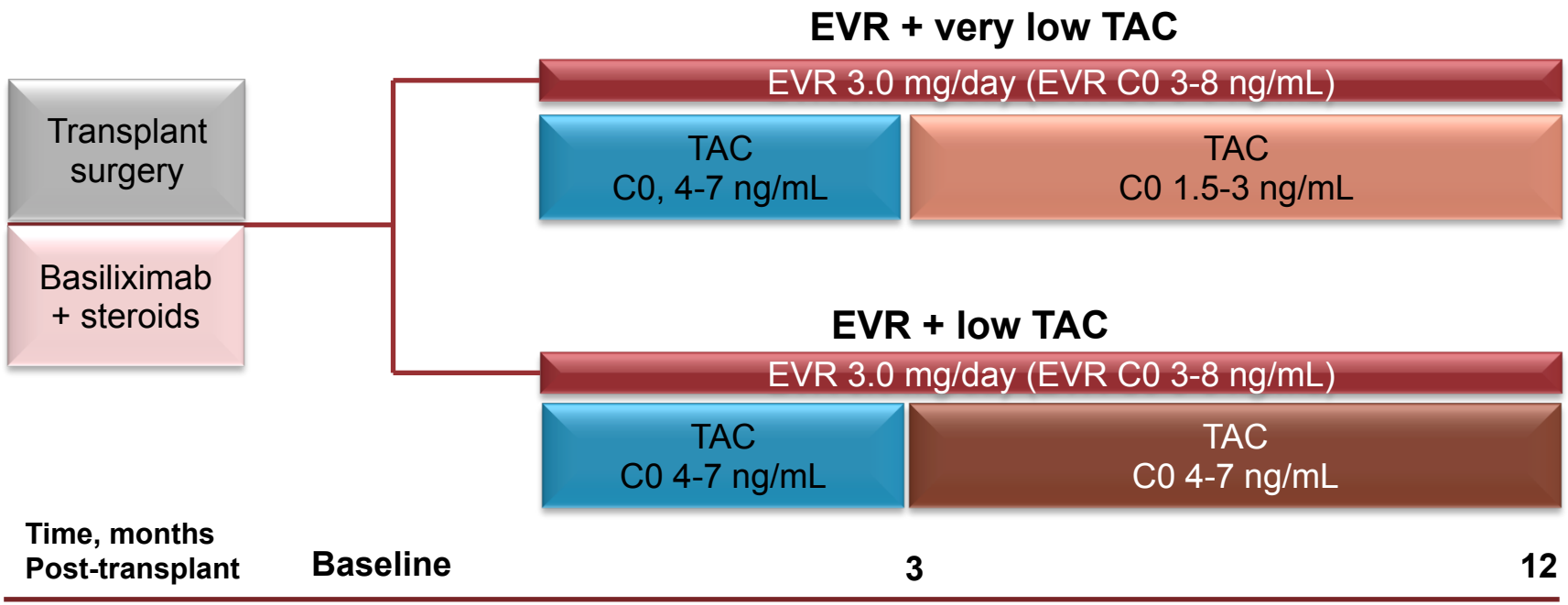
Normal	86	75	40	18
Fibrosis	122	107	55	28
Fib & Infl.	48	38	18	12
Glomer	15	8	2	0

Reprinted with permission from Cosio FG, et al. *Am J Transplant*. 2005;5(10):2464-2472.

Current Approaches to Managing Immunosuppression



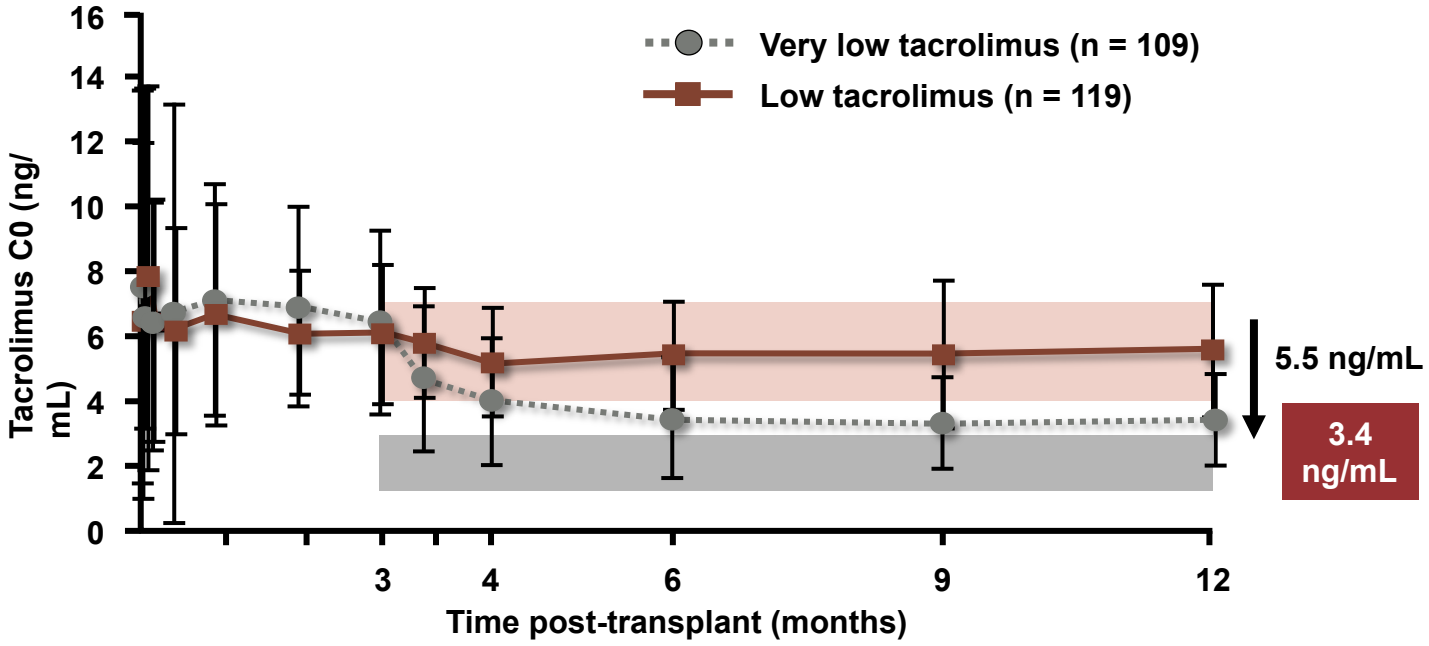
De novo TAC Minimization with Everolimus: ASSET (A2426) Study Design



Langer RM, et al. *Transpl Int.* 2012; 25(5):592−602.

De novo Everolimus Facilitates Substantial Tacrolimus Minimization

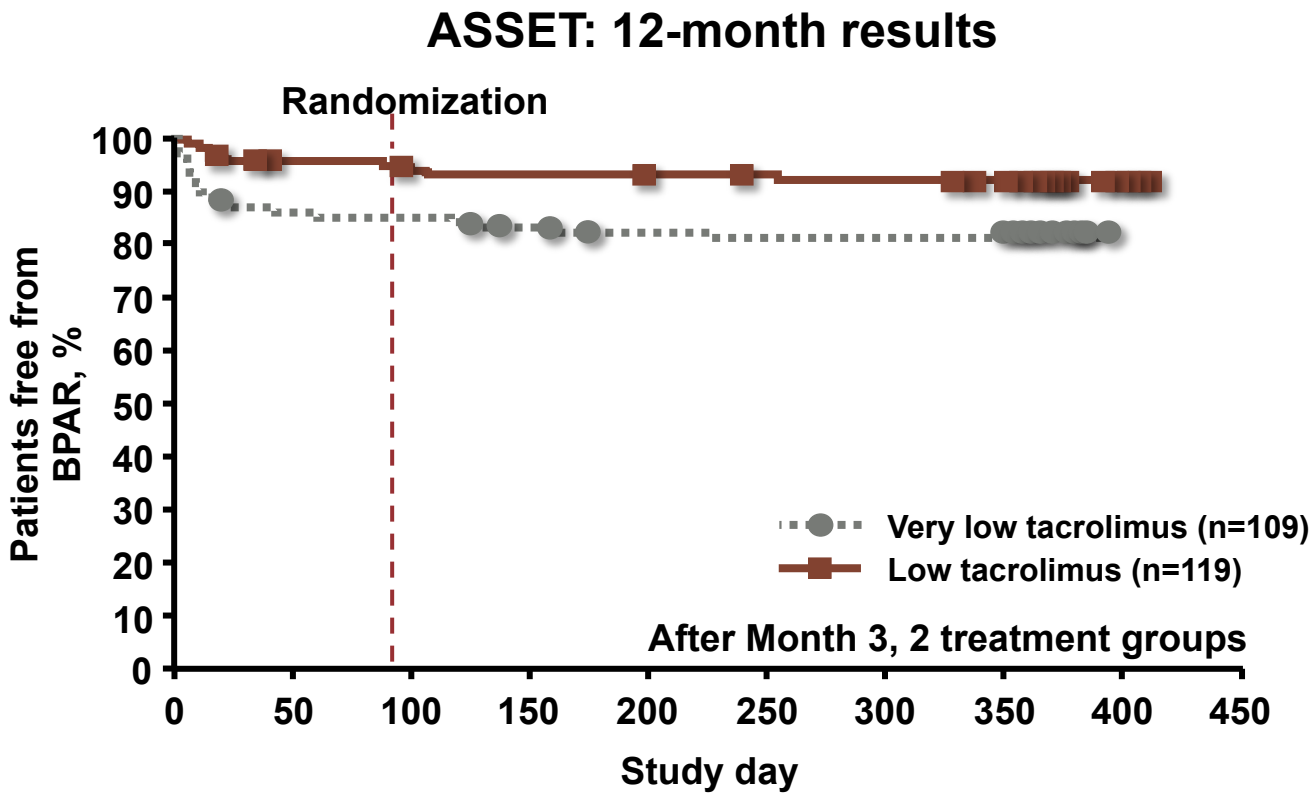
ASSET: 12 month results



Tacrolimus C0 levels were ~50% lower than in the SYMPHONY study at 12 months[1,2]

Langer RM, et al. *Transpl Int.* 2012;25(5):592−602.
Ekberg H, et al. *N Engl J Med*. 2007;357(25):2562-2575.

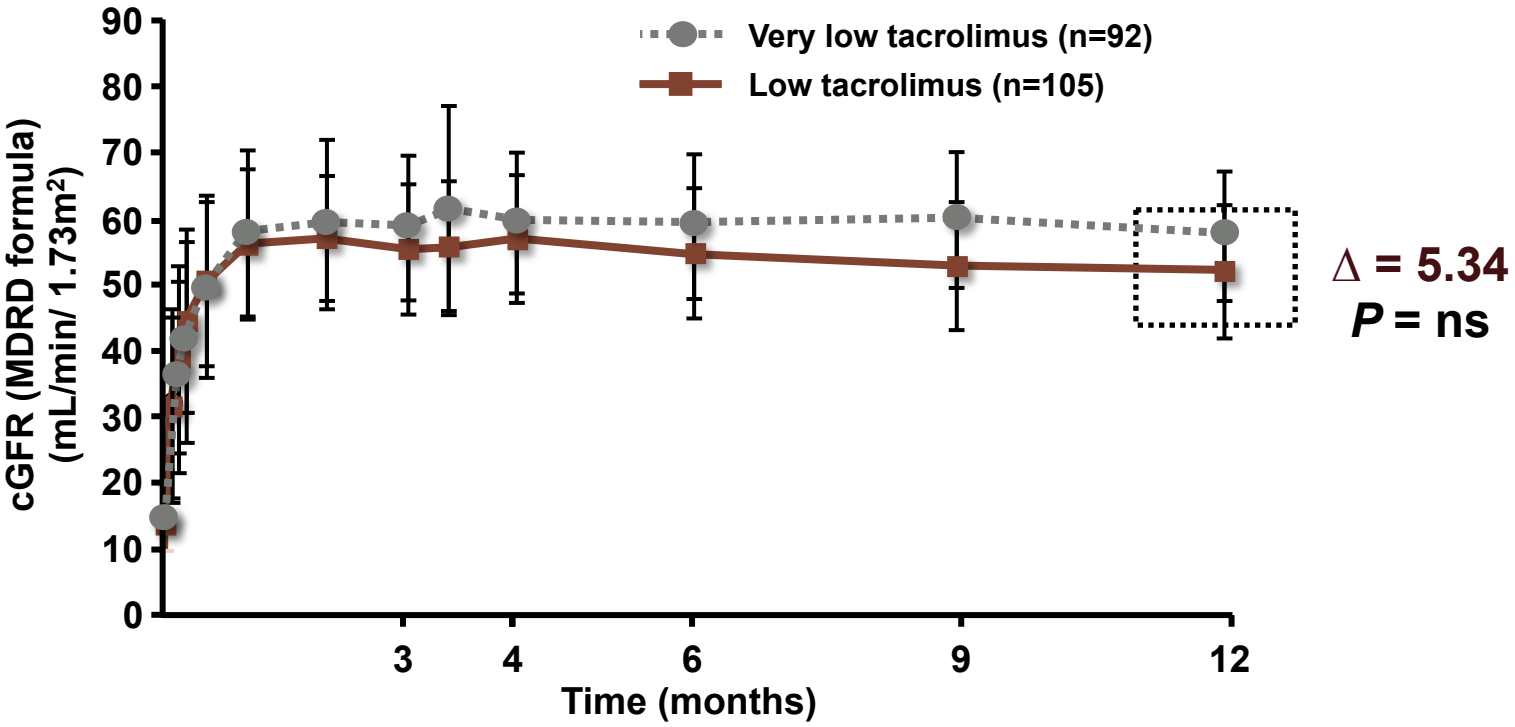
Low vs. Very Low Tacrolimus with Everolimus: Similar BPAR After Randomization at Month 3



Langer RM, et al. *Transpl Int.* 2012; 25(5):592−602.

Everolimus and Very Low Tacrolimus: Less CNI Exposure, Better Preservation of Renal Function

ASSET: 12-month results



Langer RM, et al. *Transpl Int.* 2012;25(5):592−602.

Belatacept-Based CNI Free Immunosuppression

The NEW ENGLAND JOURNAL of MEDICINE

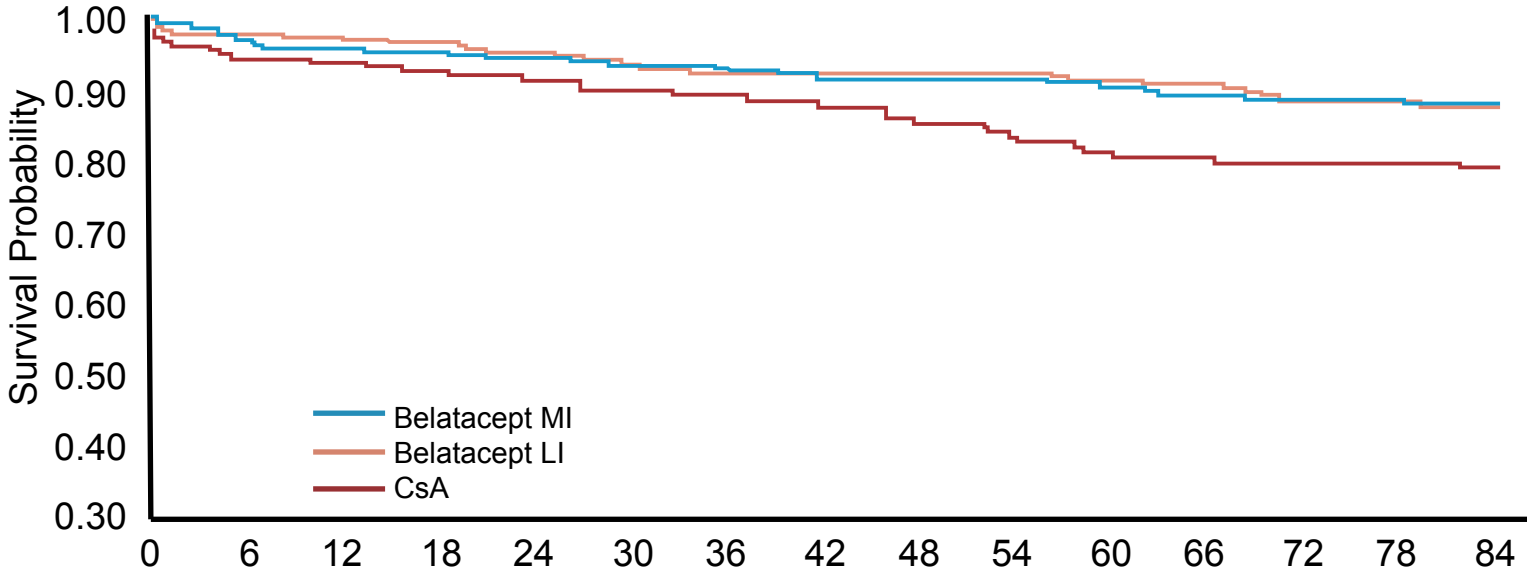
ORIGINAL ARTICLE

Belatacept and Long-Term Outcomes in Kidney Transplantation

Flavio Vincenti, M.D., Lionel Rostaing, M.D., Ph.D., Joseph Grinyo, M.D., Ph.D., Kim Rice, M.D., Steven Steinberg, M.D., Luis Gaite, M.D., Marie-Christine Moal, M.D., Guillermo A. Mondragon-Ramirez, M.D., Jatin Kothari, M.D., Martin S. Polinsky, M.D., Herwig-Ulf Meier-Kriesche, M.D., Stephane Munier, M.Sc., and Christian P. Larsen, M.D., Ph.D.

Vincenti F, et al. *N Engl J Med*. 2016;374(4):333-343.

Time to Death or Graft Loss From Randomization to Month 84



N at risk

Belatacept MI	219	212	208	206	204	202	199	153	151	149	146	142	135	131	128
Belatacept LI	226	220	218	216	213	209	204	165	161	159	152	151	142	139	137
CsA	221	208	206	202	199	197	186	137	123	117	112	107	102	100	92

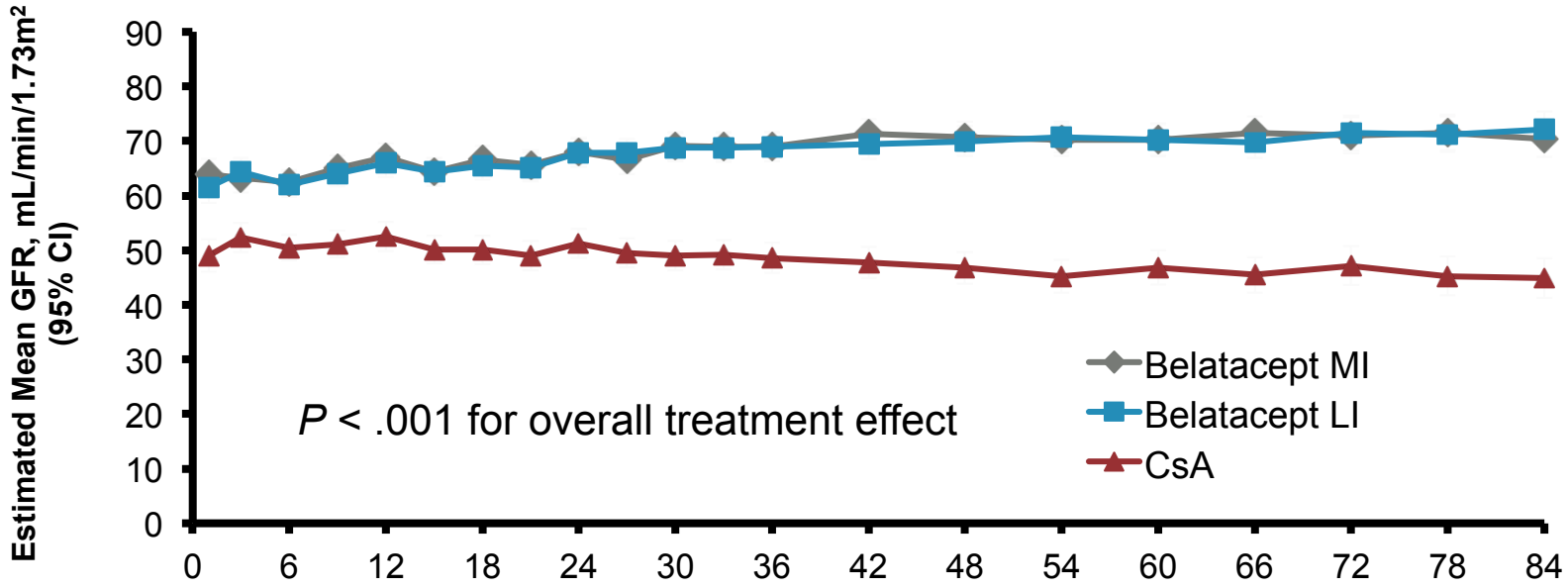
Month 60		
	P - value	HR (95% CI)
Bela MI vs. CsA	0.0100	0.521 (0.306, 0.889)
Bela LI vs. CsA	0.0045	0.477 (0.277, 0.819)

Month 84		
	P - value	HR (95% CI)
Bela MI vs. CsA	0.0225	0.573 (0.348, 0.946)
Bela LI vs. CsA	0.0210	0.570 (0.348, 0.935)

Bela = belatacept; CI = confidence interval; CsA = cyclosporine A; HR = hazard ratio; LI = less intensive; MI = more intensive.

Vincenti F, et al. *N Engl J Med*. 2016;374(4):333-343.

Estimated Mean GFR Over 84 Months: MEM Without Imputation

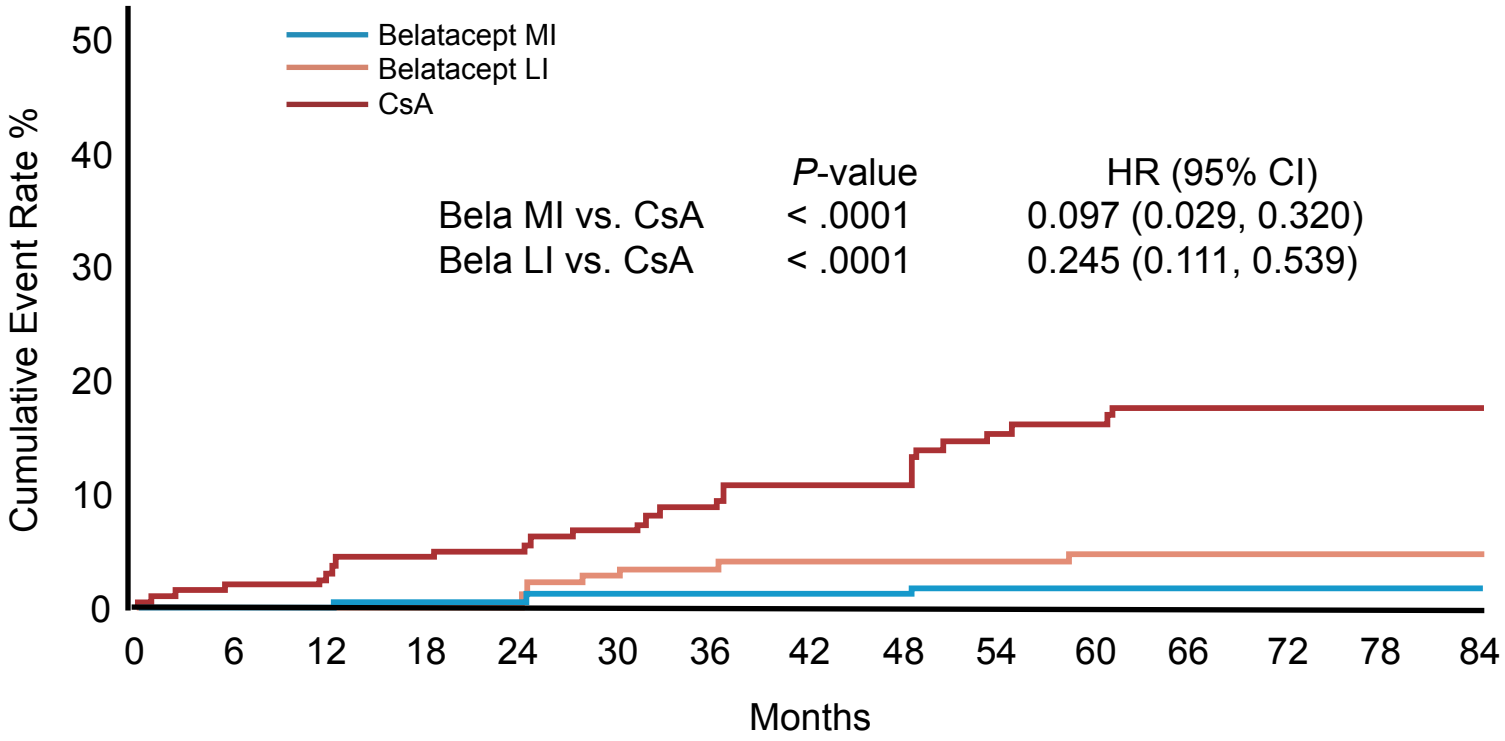


	Belatacept MI		Belatacept LI		CsA
	GFR	Difference vs. CsA	GFR	Difference vs. CsA	GFR
Month 12	67.0	14.5	66.0	13.5	52.5
Month 36	68.9	20.3	68.9	20.4	48.6
Month 60	70.2	23.3	70.3	23.4	46.8
Month 84	70.4	25.6	72.1	27.3	44.9

CsA = cyclosporine A; GFR = glomerular filtration rate; LI = less intensive; MEM = mixed effects modeling; MI = more intensive.

Vincenti F, et al. *N Engl J Med*. 2016;374(4):333-343.

Kaplan-Meier Analysis of Cumulative De Novo DSA Over Time



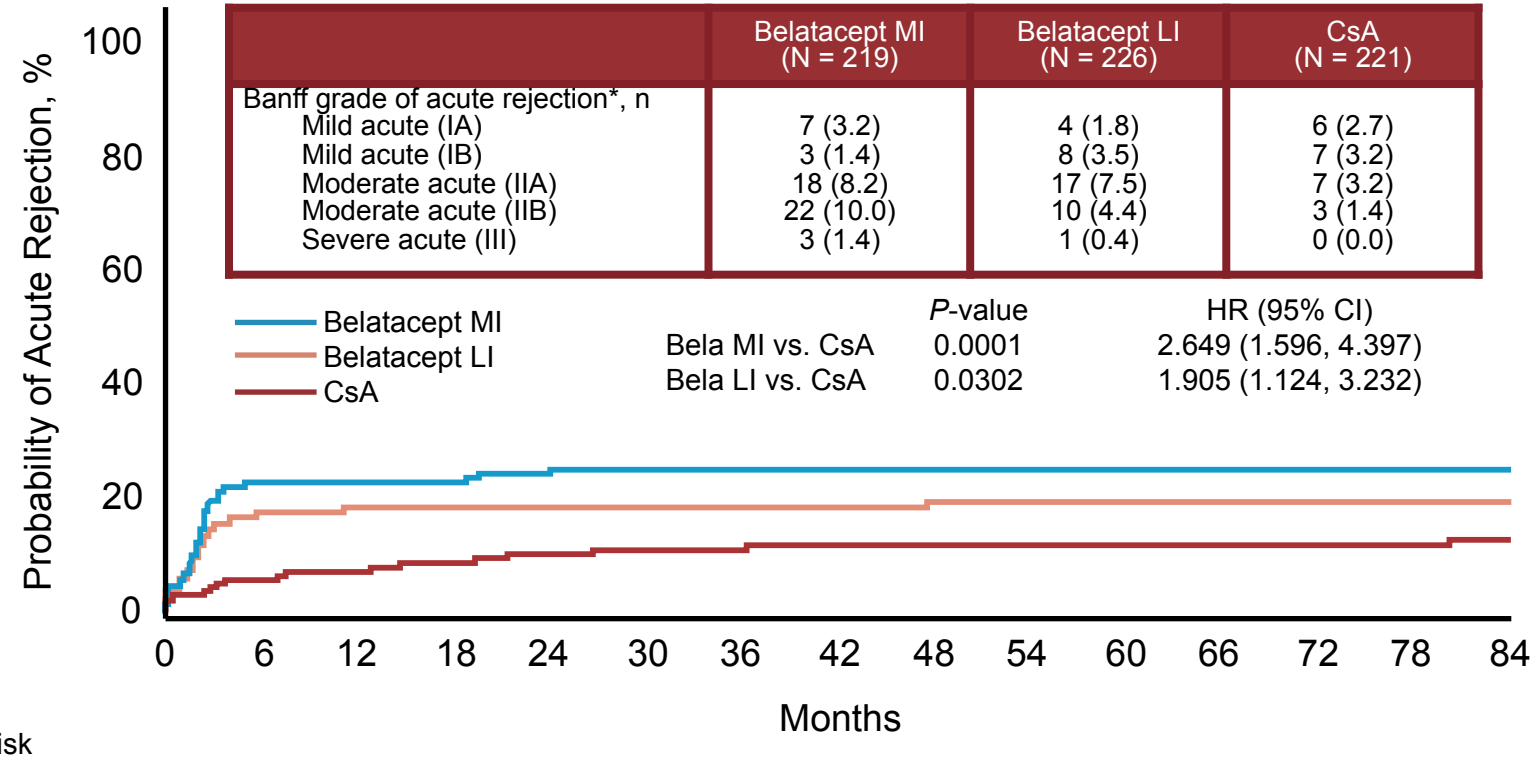
N at risk

Belatacept MI	219	182	174	168	163	158	156	148	147	144	141	136	130	127	124
Belatacept LI	226	187	183	180	178	169	165	158	154	152	145	143	138	133	130
CsA	215	186	171	159	150	143	136	124	115	108	103	97	92	90	85

Vincenti F, et al. *N Engl J Med*. 2016;374(4):333-343.

Acute Rejection

	Belatacept MI (N = 219)	Belatacept LI (N = 226)	CsA (N = 221)
Banff grade of acute rejection*, n			
Mild acute (IA)	7 (3.2)	4 (1.8)	6 (2.7)
Mild acute (IB)	3 (1.4)	8 (3.5)	7 (3.2)
Moderate acute (IIA)	18 (8.2)	17 (7.5)	7 (3.2)
Moderate acute (IIB)	22 (10.0)	10 (4.4)	3 (1.4)
Severe acute (III)	3 (1.4)	1 (0.4)	0 (0.0)



N at risk

Belatacept MI	219	154	147	144	140	137	136	128	127	125	122	117	111	108	105
Belatacept LI	226	168	164	162	160	157	155	149	144	142	137	135	130	125	122
CsA	221	180	167	156	147	141	135	123	115	110	106	101	96	94	89

For patients with an event, the time to event was defined as minimum of event date and date of last dose (transplant date for non-treated patients) plus 56 days. For patients without an event, the time to event was defined as last follow-up date for on-treatment patients, date of last dose plus 56 days for off-treatment patients, and transplant date plus 56 days for non-treated patients. Between Month 36 and Month 84, 0 belatacept MI-treated, 1 (grade IIA) belatacept LI-treated, and 2 (grade IA [n=1], grade IIA [n=1]) CsA-treated patients experienced acute rejection.

*Three patients (n=1 [grade IIA], belatacept MI; n=2, CsA [n=1, grade IA; n=1, grade IIA]) experienced acute rejection more than 56 days after treatment discontinuation.

Vincenti F, et al. *N Engl J Med*. 2016;374(4):333-343.

Why Belatacept Has Not Fulfilled Its Potential as a Transformational Immunosuppression Agent

- Higher rejection rates and histologically more severe
  - Better regimens
- PTLD
  - Not an issue with EBV + recipients and lower acute rejection
- IV administration
  - Could be advantageous for adherence
- Cost
  - Cost-effectiveness yet to be determined

Can Intragraft Inflammation be Treated?

- Can we improve current immunotherapy to suppress inflammation?
- Need novel approaches:
  - CTOT-19 use of infliximab to inhibit early inflammation in kidney transplant patients[1]
  - CTOT-21 adoptive T-reg cell infusions to control graft inflammation[2]
  - Use of anti-IL6 receptor antibody to control inflammation in in kidney transplantation[3]

1. Vincenti, F, et al. Effects of Inhibiting Early Inflammation in Kidney Transplant Patients. ClinicalTrials.gov Identifier: NCT02495077. 2015.
2. Heeger P, et al. Effects of Inhibiting Early Inflammation in Kidney Transplant Patients. ClinicalTrials.gov Identifier: NCT02495077. 2015.
3. Vincenti F, et al. Treg Adoptive Therapy in Subclinical Inflammation in Kidney Transplantation (CTOT-21) Clinical Trials Identifier: NCT02711826. 2016.

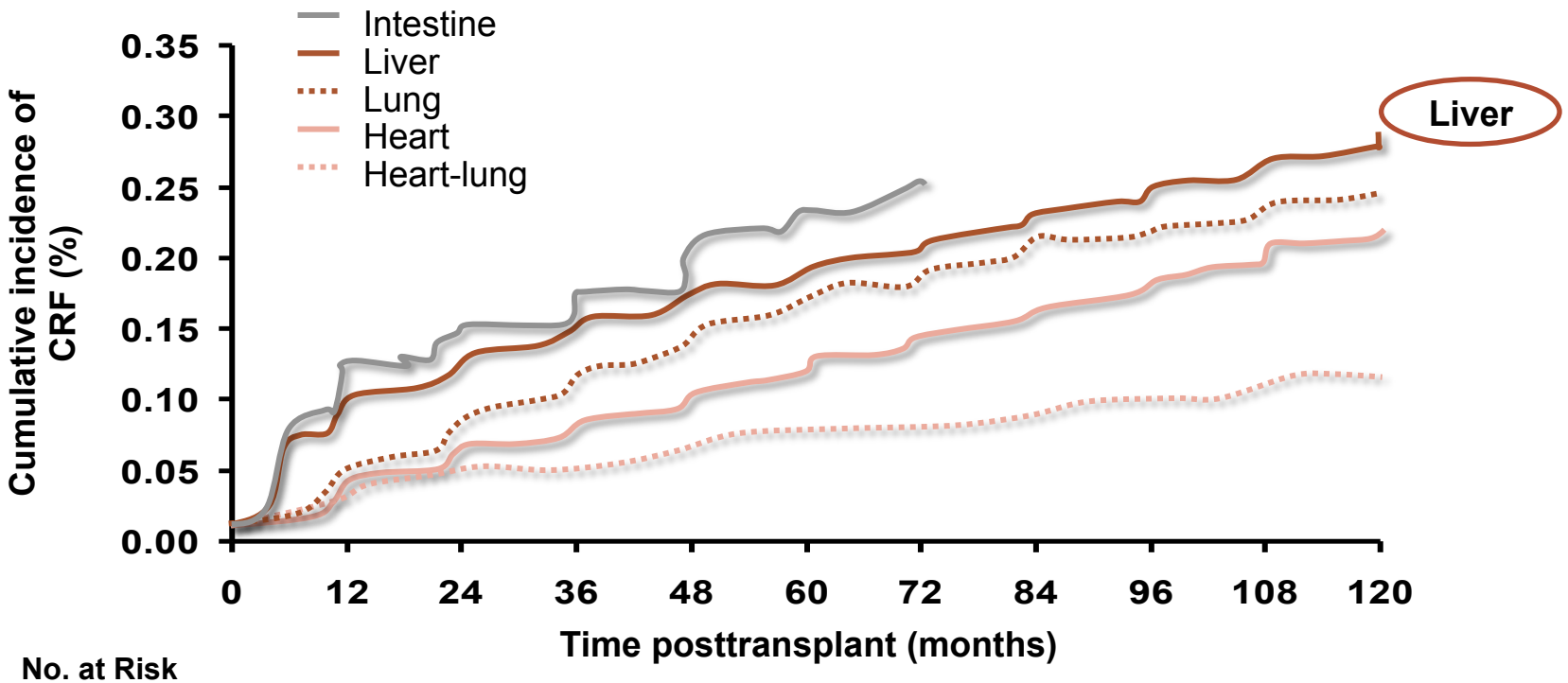
Immunosuppression and Monitoring Considerations in Liver Transplantation

Chronic Renal Failure after Transplantation of a Nonrenal Organ

- Data from a registry of patients with end-stage renal disease were reviewed in order to estimate the cumulative incidence of chronic renal failure and associated risk among 69,321 persons who received nonrenal transplants in the US between 1990 and 2000
- At 36 months, chronic renal failure developed in 11,426 patients (16.5%)
- Of these patients, 3,297 (28.9%) required maintenance dialysis or renal transplantation

Ojo AO, et al. *N Engl J Med*. 2003;349(10):931-940.

Liver Transplant Patients are at a High Risk of Renal Failure



No. at Risk											
Heart-lung	576	375	295	219	194	156	133	107	72	46	30
Heart	24024	19885	17238	14687	12341	10022	7997	6104	4526	3096	1991
Intestine	228	152	110	84	57	33	23	13	8	5	5
Liver	36849	28495	24041	19508	15724	12564	9844	7345	5292	3614	2261
Lung	7643	5633	4316	3184	2327	1629	1136	745	468	258	133

CRF = chronic renal failure

Ojo AO, et al. *N Engl J Med.* 2003;349(10):931-940.

Chronic CNI Therapy Decreases Renal Function

The elephant in the room

Chronic CNI Therapy Decreases Renal Function Over Time In Liver Transplant Recipients

Renal function by stage of kidney disease in liver transplant patients (n = 1502)					
Stage of Kidney Disease	GFR (mL/min/1.73 m^2)	Before Liver Transplantation, % (n)	After Liver Transplantation, % (n)		
			1 Month	12 Months	60 Months
1	≥90	54.3 (819)	15.9 (240)	7.7 (117)	5.7 (86)
2	60-89	34.9 (526)	36.4 (549)	41.1 (619)	36.6 (552)
3	30-59	9.5 (143)	43.9 (662)	48.7 (734)	52.7 (795)
4	15-29	1.1 (17)	3.5 (53)	2.4 (36)	3.7 (56)
5	<15 and HD	0.2 (3)	0.3 (4)	0.13 (2)	1.3 (19)

Karie-Guigues S, et al. *Liver Transpl*. 2009;15(9):1083-1091.

Can Experiences in Kidney Transplantation Inform Liver Transplantation?

Demographic characteristics cannot be modified and current trends will probably continue

Therefore, can we modify immunosuppression?

Most patients currently receive a CNI after liver transplant, similar to the situation in kidney transplantation

So, are there lessons to be learned from the kidney transplant setting?

CNI = calcineurin inhibitor

Can Experiences in Kidney Transplantation Inform Liver Transplantation?

Immunosuppressive regimen is highly important after kidney transplant: CNI nephrotoxicity is almost universal[1]

mTORis act via a different signalling pathway to CNIs and have potent immunosuppressive effects via inhibition of T-cell expansion, proliferation and migration[2–5]

Early rather than late conversion to an mTORi immunosuppressive regimen is more beneficial in preserving renal function[6]

Everolimus with CNI minimization has been investigated in several trials of kidney transplant recipients in relation to efficacy and renal function[7,8]

mTORi = mammalian target of rapamycin inhibitor

1. Nankivell BJ, et al. Transplantation 2004;78(4):557–565; 2. Ponticelli C. *Transpl Int* 2008;21(1):2–10; 3. Song J, et al. *Cell Mol Immunol* 2008;5(4):239–247; 4. Finlay D, Cantrell D. *Ann N Y Acad Sci* 2010;1183:149–57; 5. Colombetti S, et al. *J Immunol* 2006;176(5):2730–2738; 6. Flechner SM, et al. *Clin Transplant* 2008;22(1):1–15; 7. Tedesco-Silva Jr H, et al. *Am J Transplant* 2010;42(10):1659–66; 8. Nashan B, et al. *Transplantation* 2004;78(9):1332–1340.

Calcineurin Inhibitor-Free Mycophenolate Mofetil/Sirolimus Maintenance in Liver Transplantation

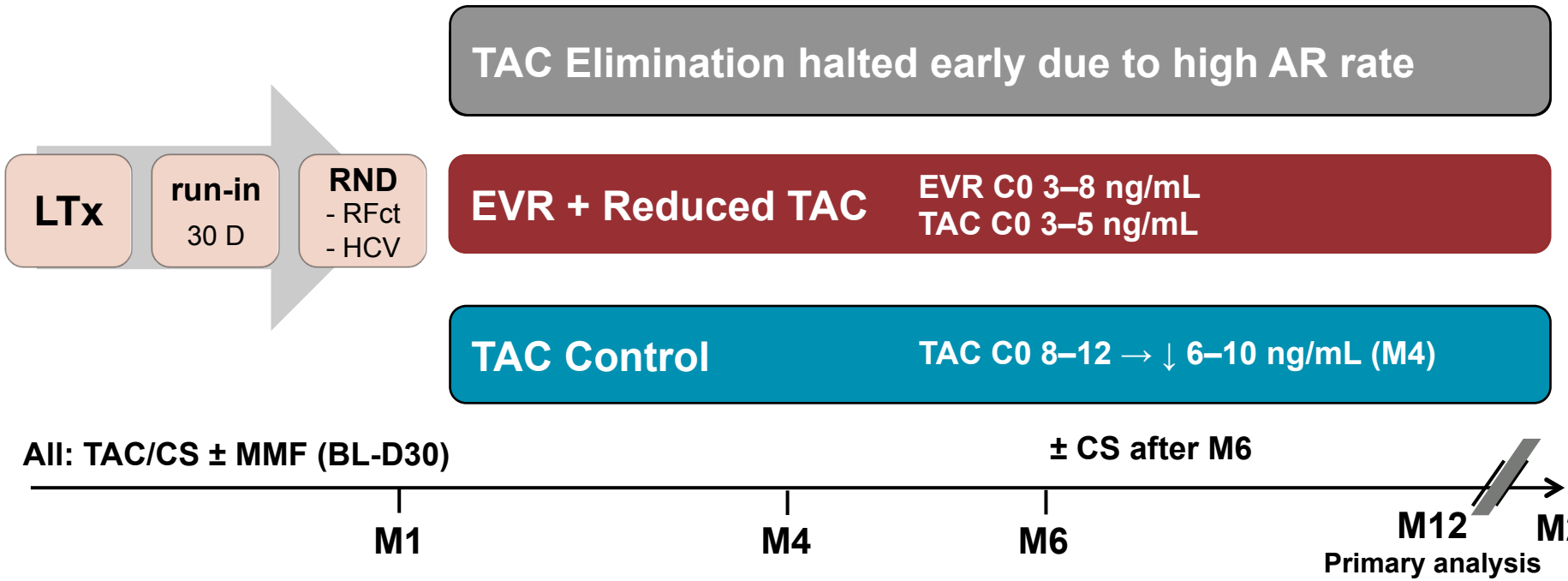
The Randomized Spare-the-Nephron Trial

- First mTor used in liver transplantation
- Improved renal function
- Intolerability

Teperman L, et al. *Liver Transpl*. 2013;19(7):675-689.

H2304: Study Design

A multicenter, open-label, randomized, controlled study to evaluate the efficacy and safety of EVR to eliminate or reduce TAC in de novo liver transplant recipients

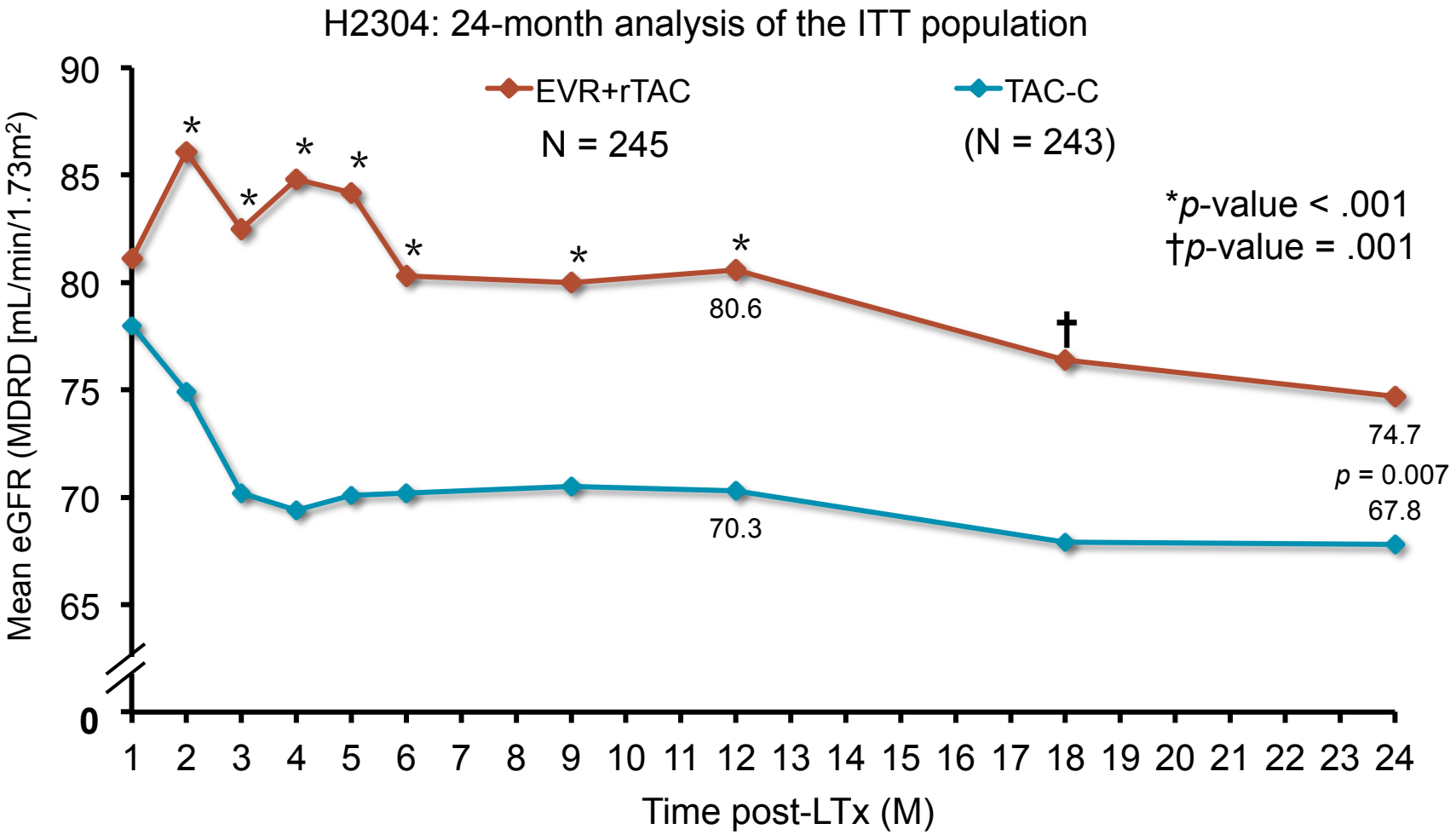


Enrollment into TAC-WD arm was stopped due to higher rejection rates and protocol was amended based on DMC recommendation (Apr 2010)

AR = acute rejection; BL = baseline; C0 = concentration; CS = corticosteroids; d = day; EVR = everolimus; HCV = hepatitis C virus; M = month; MMF = mycophenolate mofetil; LTx = liver transplantation; RND = randomization; RFct = renal function; TAC = tacrolimus.

1. De Simone P, et al. *Am J Transplant*. 2012;12(11):3008–30020.
2. Saliba F, et al. *Am J Transplant*. 2013 Jul;13(7):1734-1745.

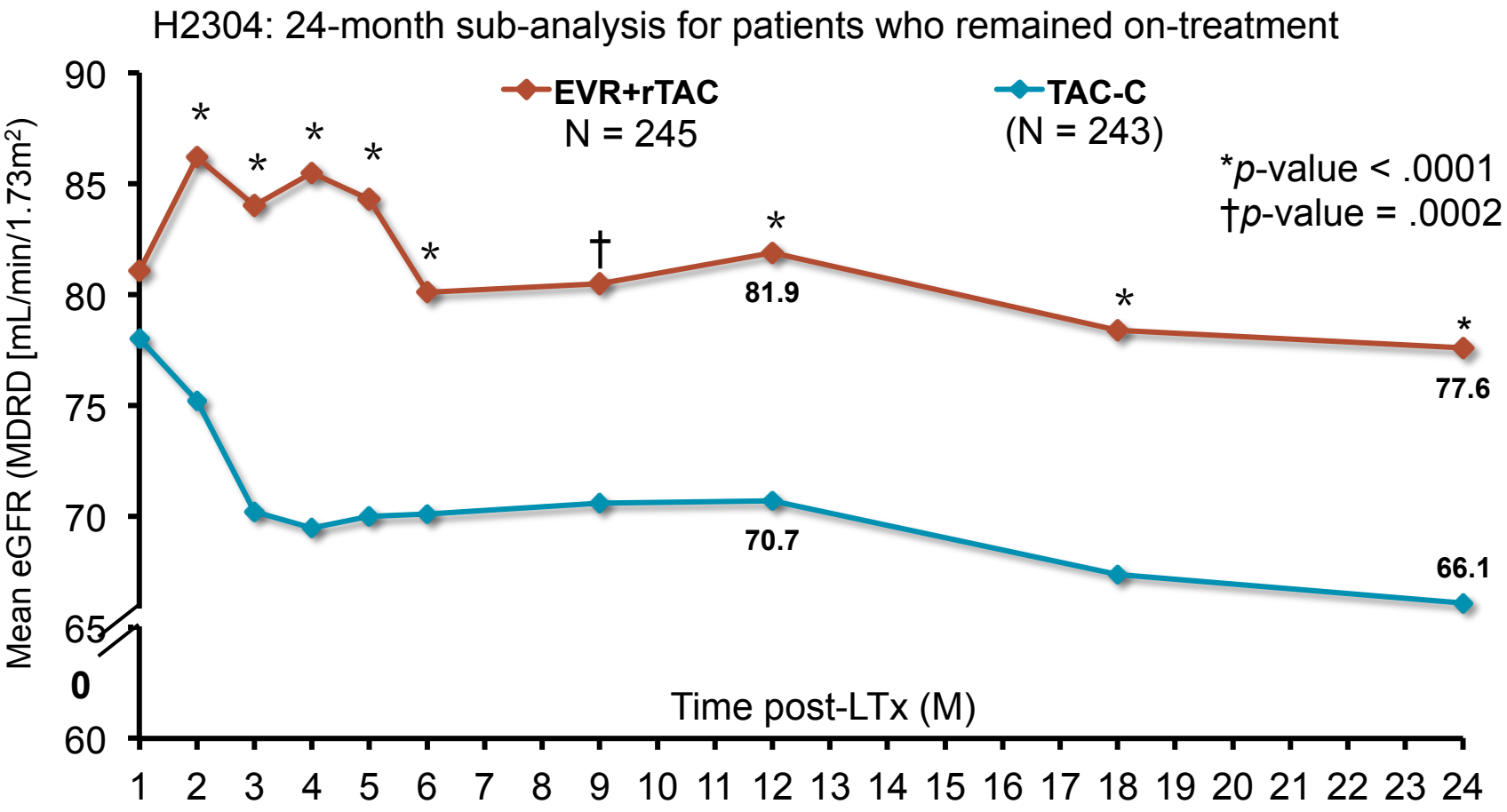
H2304: Significantly Better Renal Function with EVR + rTAC vs TAC-C is Observed 2M After Transplantation and Was Sustained Until 24 Months



eGFR = estimated glomerular filtration rate; EVR = everolimus; ITT = intent-to-treat; LTx = liver transplantation; M = month; MDRD = Modification of Diet in Renal Disease; rTAC = reduced tacrolimus; TAC-C = tacrolimus control.

Saliba F, et al. *Am J Transplant*. 2013 Jul;13(7):1734-1745.

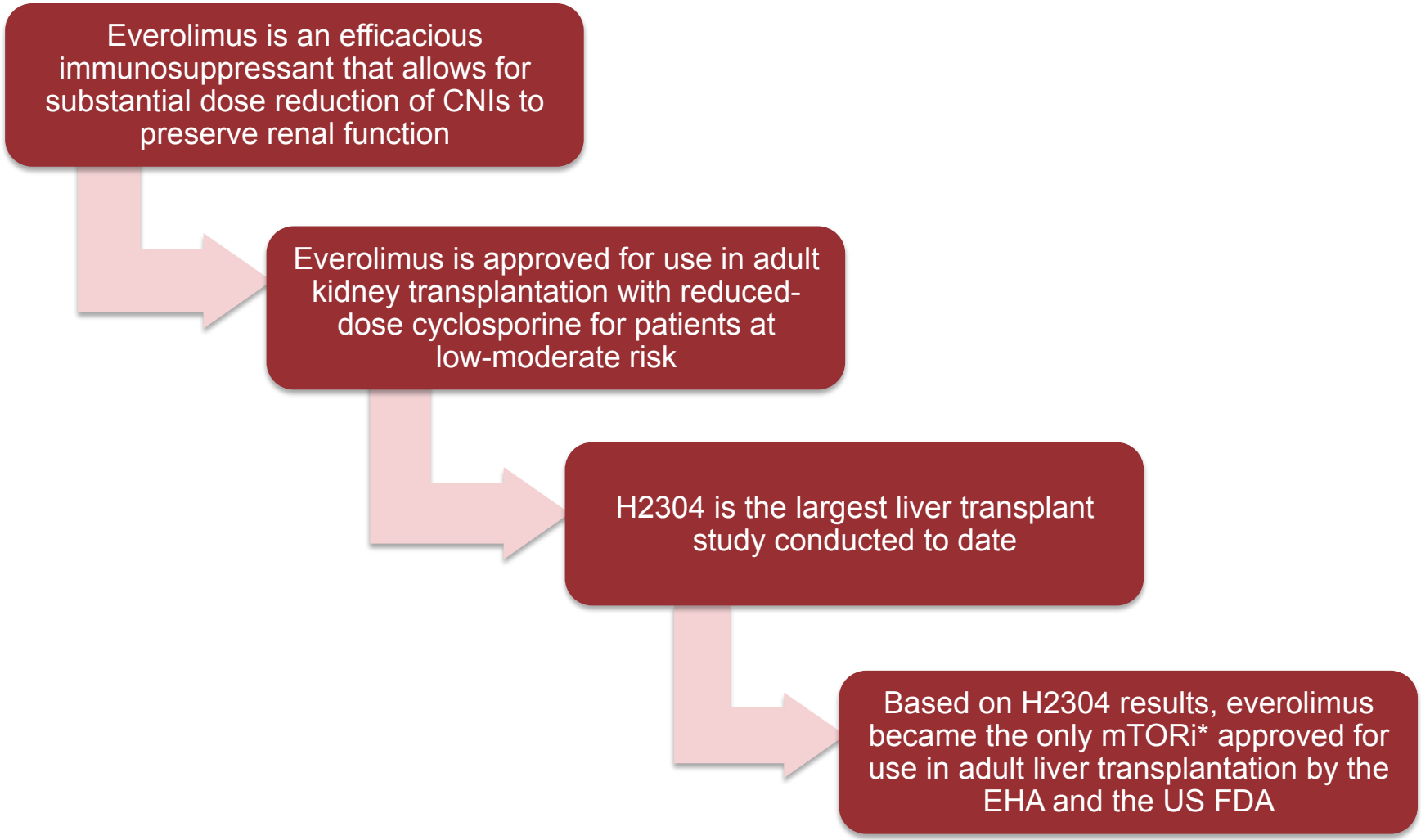
H2304: The Difference in Renal Function is Even More Pronounced in Patients Who Remained On-Treatment



eGFR = estimated glomerular filtration rate; EVR = everolimus; LTx = liver transplantation; MDRD = Modification of Diet in Renal Disease; M = month; rTAC = reduced tacrolimus; TAC-C = tacrolimus control

Saliba F, et al. *Am J Transplant*. 2013;13(7):1734-1745.

H2304 Study: Conducted to Address Key Unmet Needs in Liver Transplant Recipients



*In combination with reduced-dose tacrolimus.; EHA = European Health Authorities

Fischer L, et al. *Transplantation*. 2015;99(7):1455-1462.

Protecting Renal Function Following Liver Transplant Requires a Multifactorial Approach

- Optimized perioperative management including fluid management
- Avoiding nephrotoxic drugs
- Biological agents for induction or maintenance
  - ATG, basiliximab
- Immunosuppressive regimens
  - Reducing
  - Delaying
  - Withdrawing
  - Avoiding

  } **Calcineurin inhibitors**
- Replacement options
  - Mycophenolate
  - Everolimus

ATG = anti-thymocyte globulin

Levitsky J, et al. *Am J Transplant*. 2016 Mar 1. [Epub ahead of print].

Chart: Lilly Chang

Patient: 65 year old Asian female

Clinical Workup

Menu

Calendar

Tests

Presentation:

3cm hepatocellular carcinoma

-5’1”, 90 lbs
-Moderate ascities
-Creatinine is 3
-MELD Score is 35

Audience Response

What immunosuppresion would you use initially?

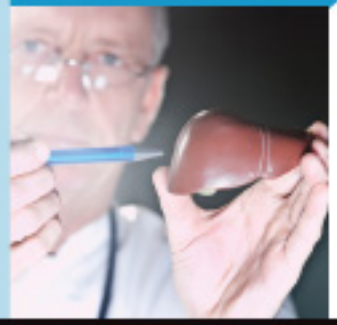
A. CNI inhibitor
B. Everolimus
C. Basiliximab alone
D. Basiliximab with mycophenolate mofetil and steroids

Audience Response

What immunosuppression would you use for maintenance?

A. High dose CNI
B. Moderate dose CNI
C. Everolimus therapy with low dose CNI
D. Belatacept

The Challenges of Adherence



Menu

Calendar

Tests

Chart: Susan Robinson

Patient: 37 year old Caucasian female

Medical History

HTN since age 11
Lifelong history of chronic kidney disease
Diagnosed with ESRD in early 20's.
Bilateral nephrectomy at age 25.
Dialysis for 2 years and kidney transplant at age 27.

-5'7", 130 lbs
-BP, 150/90mm Hg

Current medications
Calcineurin inhibitor
Mycophenolic acid
Prednisone
Lisinopril

Current life situation:
Lives with and cares for mother
Part-time job as bookkeeper
Attending graduate school for MBA

Describes busy schedule and often forgets to take medications
Missed last lab appointment for blood work

Reported medication side-effects:

Intermittent stomach problems
Occasional headaches

Audience Response

One of the most significant self-reported factors for patient nonadherence has been shown to be:

A. Medication side effects
B. Complexity of dosing
C. Lack of social support
D. Poor memory

Self-Reported Nonadherence to Immunosuppressants

- Renal transplant recipients (N = 250)
  - 46% adherent
  - 48% reported timing deviations
  - 18% nonadherent in last 4 weeks

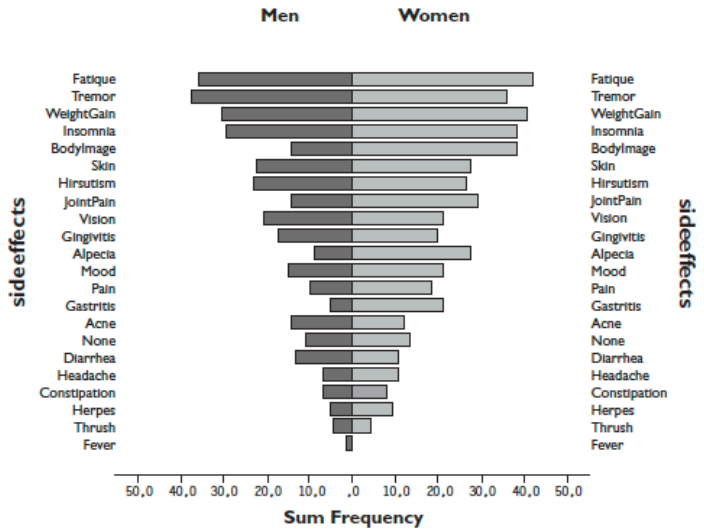


Fig. (1). The reported frequency of various symptoms and side effects that may be related to the immunosuppressive therapy divided by men and women (n=250).

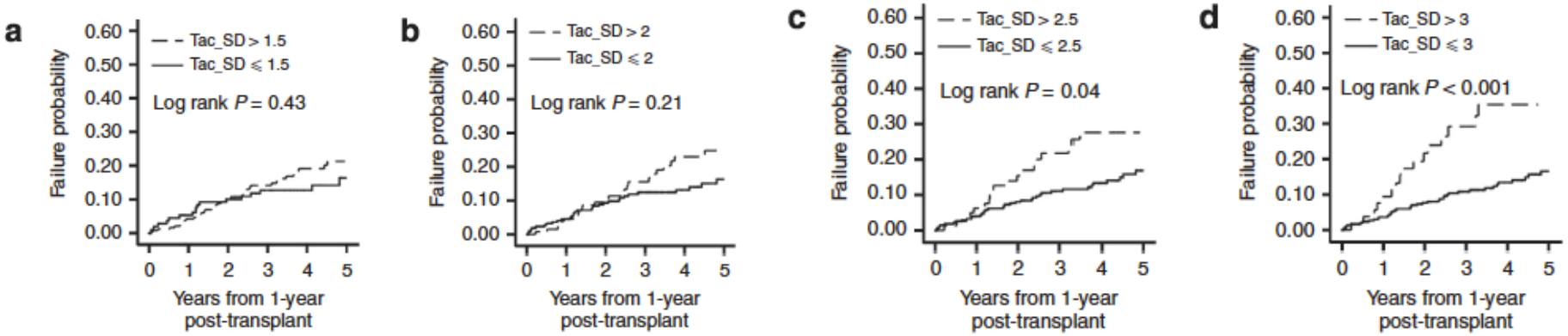
Most significant factor for nonadherence was lack of social support (p = .022)

Lennerling A, et al. *Open Nurs J*. 2012;6:41-46.

Use of Drug Level Monitoring (Intra-Patient Variability) to Assess Under-immunosuppression/Adherence

356 patients, measured tacrolimus variability while on stable dose ("tacSD" = tacrolimus standard deviation), median follow-up 3.72 years

Composite end point: late allograft rejection, transplant glomerulopathy, or graft loss (including death)



For every 1-unit increase in TacSD, a 27% increase in composite end point [HR 1.27 (95% CI 1.03-1.56)]

Sapir-Pichhadze R, et al. *Kidney Int*. 2014;85(6):1404-1411.

Nonadherence to Post-Transplant Immunosuppression

- Study to identify adult patients most at risk for non-adherence (N = 572)
- Over 10 years, 50% reported non-adherence
- Non-adherence was reported highest in the 2-5 year post-transplant phase (56%)
- The highest immune-suppressant nonadherence rates
  - Divorced (76%)
  - History of substance or alcohol use (61%)
  - Mental health needs (60%)
  - Those who missed clinic appointments (83%)
  - Did not maintain medication logs (58%)

Lamba S, et al. *Clin Transplant.* 2012;26(2):328-335.

Engage Patients to Improve Adherence

- Patients have different barriers to medication adherence
  - Side effects, complex dosing regimens, work schedules, forgetfulness, life circumstances
- Discuss and tailor interventions to individual risk factors
- Encourage support groups – local or online
- Suggest technologies to assist in adherence (reminder systems, etc)

Low JK, et al. *Nephrol Dial Transplant*. 2015;30(5):752-761.

Using New Technology to Improve Outcomes

- Adherence
- Molecular-based diagnosis
- Facilitating Cell Therapy

Technology and Adherence

New approaches to medication adherence include sensor chips that can be incorporated into any pill and signal when a pill has been ingested.

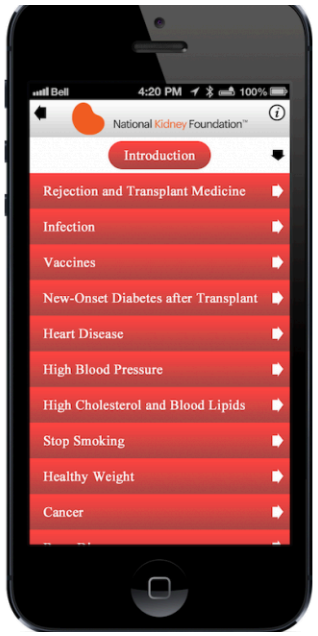
Adherence Efforts Go High-Tech

Social media, mobile apps and other technologies may help patients with medication adherence and self-management skills, and improve outcomes

Macready N. *Am J Transplant*. 2012;12(9):2263-2264.

Apps for Information and Adherence

- National Kidney Foundation Apps
- General information, dietary information, reminders
- Links to online and local support groups

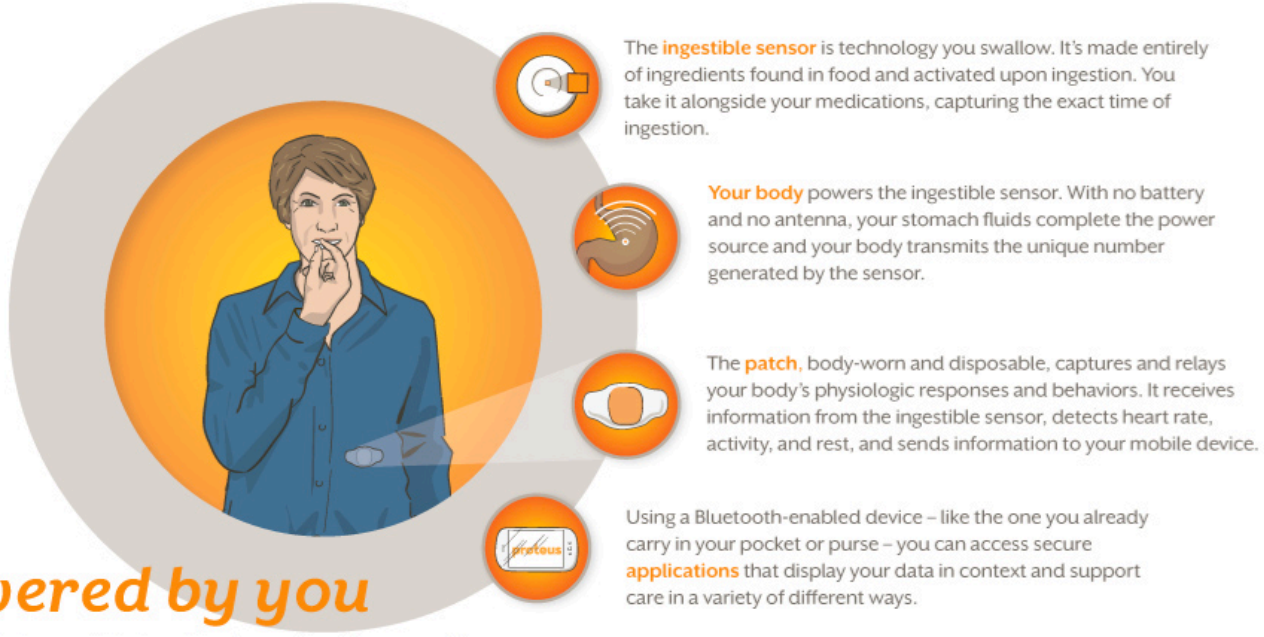


National Kidney Foundation Website: https://www.kidney.org/apps/patients/care-after-kidney-transplant-app. Accessed June 7, 2016

Technology to Assist with Adherence

Proteus Digital Health

Ingestible sensors alert doctors when a pill is taken



The **ingestible sensor** is technology you swallow. It's made entirely of ingredients found in food and activated upon ingestion. You take it alongside your medications, capturing the exact time of ingestion.

Your body powers the ingestible sensor. With no battery and no antenna, your stomach fluids complete the power source and your body transmits the unique number generated by the sensor.

The **patch**, body-worn and disposable, captures and relays your body's physiologic responses and behaviors. It receives information from the ingestible sensor, detects heart rate, activity, and rest, and sends information to your mobile device.

Using a Bluetooth-enabled device – like the one you already carry in your pocket or purse – you can access secure **applications** that display your data in context and support care in a variety of different ways.

Proteus Digital Health. http://proteusdigitalhealth.com/technology/

Social Media to Aid Adherence

Health tips, reminders, support groups, Q&A

- Fox Chase Cancer Center
  - YouTube instructional videos
- Penn Medicine
  - YouTube videos, discussion forums
- St. Joseph's Hospital and Medical Center in Phoenix
  - Twitter for tip of the day
- The University of Maryland Medical Center
  - Twitter, Facebook, YouTube

Pistritto, S. Helping Patients Adhere to Medication Compliance with Social Media. April 19, 2012. Website: http://mobile.phillyadnews.com/i/65026-may-june2012/3

Benjamin R. *Public Health Rep*. 2012;127(1):2–3.

Improved Adherence via Mobile Technology

- Facilitating active participation in self-care remains an important goal in the current health care and patient community
- Technology-based approaches represent a promising way to address non-participation in adolescent patients
- Cellphones, text messaging, and internet-based tools are widely used in the adolescent population among all socio-economic groups
- Improved adherence and outcomes for pediatric liver transplant recipients by using text messaging

McKenzie RB, et al. *J Particip Med*. 2015;7. pii: e7

The Use of Precision Medicine

Is it time to introduce it in transplantation?

kSORT (Kidney Solid Organ Response Test) Rejection

Application of the kSORT blood assay for the non-invasive prediction of histological

kSORT Validated in Pediatric and Adult Populations, LD and DD Recipients; Independent of Rx

OPEN ACCESS Freely available online

PLOS | MEDICINE

The kSORT Assay to Detect Renal Transplant Patients at High Risk for Acute Rejection: Results of the Multicenter AART Study

Silke Roedder[1☯], Tara Sigdel[1☯], Nathan Salomonis[2☯], Sue Hsieh[1], Hong Dai[3¤a], Oriol Bestard[4], Diana Metes[5], Andrea Zeevi[5], Albin Gritsch[6], Jennifer Cheeseman[7], Camila Macedo[5], Ram Peddy[3], Mara Medeiros[8], Flavio Vincenti[1], Nancy Asher[1], Oscar Salvatierra[9], Ron Shapiro[5], Allan Kirk[7¤b], Elaine Reed[6], Minnie M. Sarwal[1*]

N = 558 biopsy matched blood samples profiled by QPCR

8 programs; US, EU, Mexico

ADULT and PEDS

N = 367 biopsy matched blood samples profiled by QPCR

12 programs; US, PEDS

doi: 10.1111/j.1600-6143.2012.04253.x

A Peripheral Blood Diagnostic Test for Acute Rejection in Renal Transplantation

L. Li[a,b,†], P. Khatri[b,†], T. K. Sigdel[a,b,†], T. Tran[a,b], L. Ying[b], M. J. Vitalone[a,b], A. Chen[b], S. Hsieh[a,b], H. Dai[a,b], M. Zhang[b], M. Naesens[b], V. Zarkhin[b], P. Sansanwal[a], R. Chen[b], M. Mindrinos[d], W. Xiao[e], M. Benfield[f], R. B. Ettenger[g], V. Dharnidharka[h], R. Mathias[i], A. Portale[i], R. McDonald[k], W. Harmon[l], D. Kershaw[m], V. M. Vehaskari[n], E. Kamil[o], H. J. Baluarte[p], B. Warady[q], R. Davis[d], A. J. Butte[b], O. Salvatierra[b,c] and M. M. Sarwal[a,b,*]

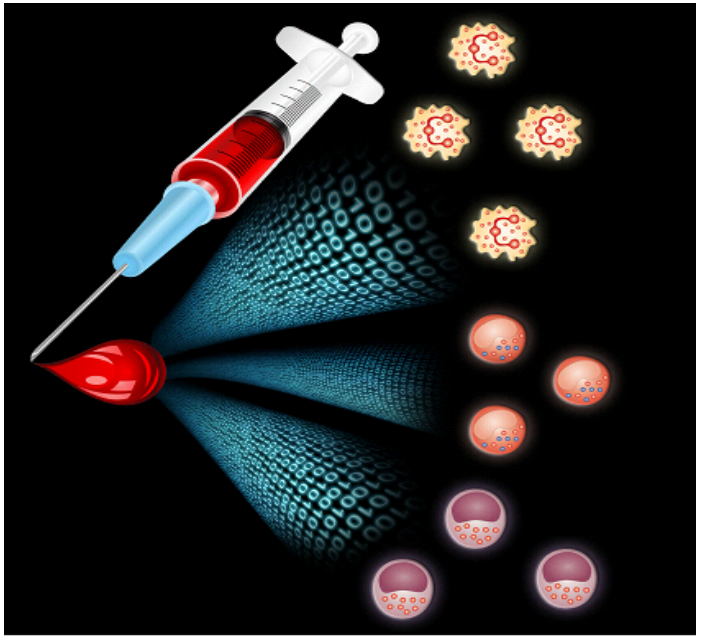
study from 12 US pediatric transplant programs. A total of 367 unique human PB samples, each paired with a graft biopsy for centralized, blinded phenotype classification, were analyzed (115 acute rejection (AR), 180 stable and 72 other causes of graft injury). Of the differentially expressed genes by microarray, Q-PCR analysis of a five gene-set (*DUSP1, PBEF1, PSEN1, MAPK9* and *NKTR*) classified AR with high accuracy. A logistic regression model was built on independent training-set (n = 47) and validated on independent test-set (n = 198)samples, discriminating AR from STA with 91% sensitivity and 94% specificity and AR from all

Roedder S, et al. *PLoS Med*. 2014;11(11):e1001759; Li L, et al. *Am J Transplant*. 2012;12(10):2710-2718.

kSORT (Kidney Solid Organ Response Test)

The answer in a drop of blood.....

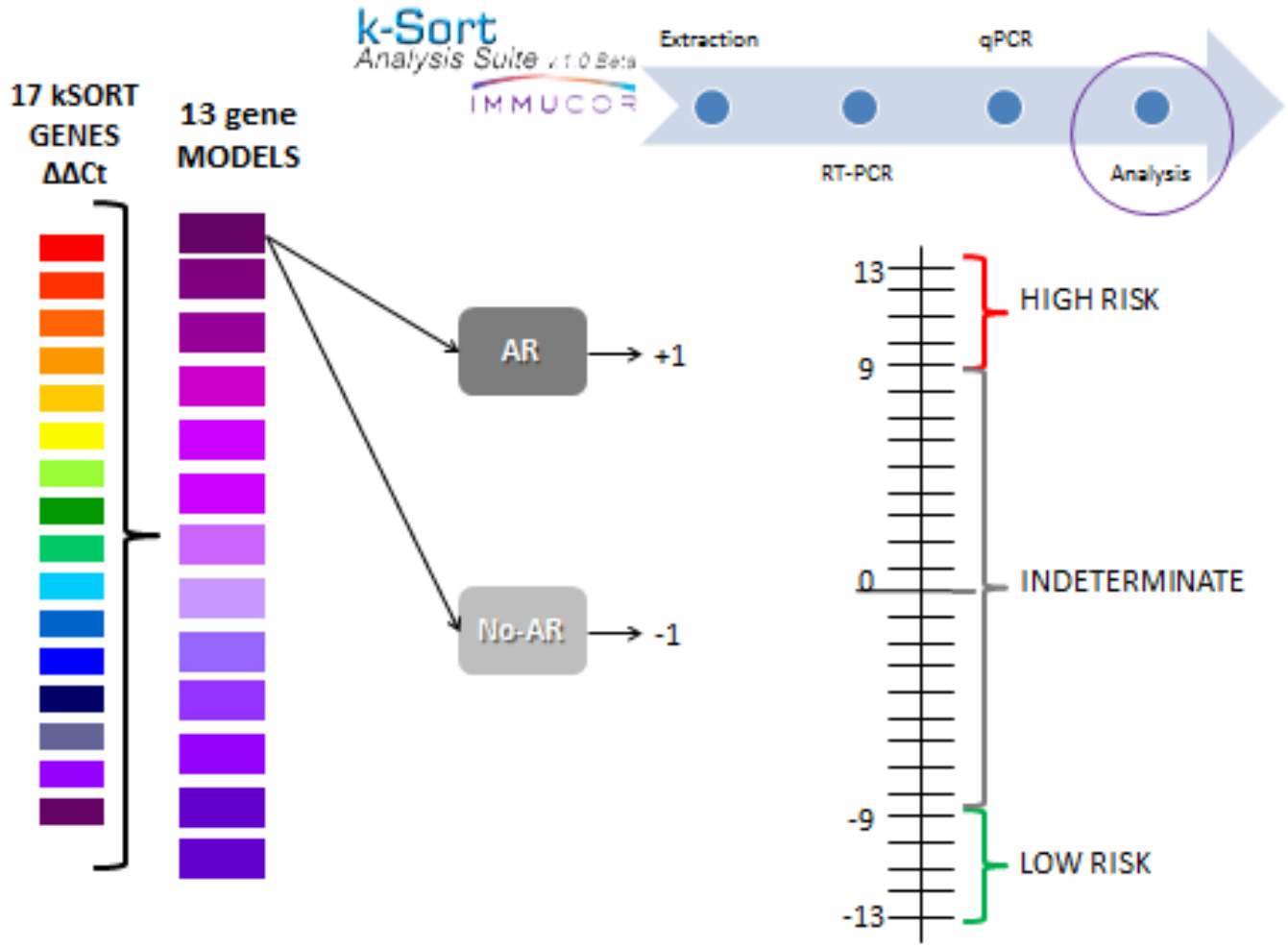
17 gene PCR test measuring graft immune activation by RNA isolated from whole blood



CFLAR, DUSP1, IFNGR1, ITGAX, MAPK9, NAMPT, NKTR, PSEN1,CEACAM4, EPOR, GZMK, RARA, RHEB, RXRA, SLC25A37, RNF130, RYBP

Roedder S, et al. *PLoS Med*. 2014;11(11):e1001759; Li L, et al. *Am J Transplant*. 2012;12(10):2710-2718.

K-SORT Analysis



Roedder S, et al. *PLoS Med*. 2014;11(11):e1001759; Li L, et al. *Am J Transplant*. 2012;12(10):2710-2718.

Facilitating Cell Therapy

- The experimental Facilitating Cell Therapy involves taking stem cells from the kidney donor and grafting them into the transplant recipient's bone marrow at the time of transplant
- The hematopoietic stem cell-based immunological tolerance protocol is in the final stages of a successful FDA Phase II clinical trial in living donor kidney transplant recipients that has resulted in graft survival without the need for lifelong immunosuppression

Leventhal J, et al. *Clin Pharmacol Ther*. 2013;93(1):36-45.

Studies in Progress

- Massachusetts General Hospital[1]
  - Examine the safety and effectiveness of a combination kidney and bone marrow transplant from a haplo-identical related donor.
- University of California at San Francisco[2]
  - Donor-Alloantigen-Reactive Regulatory T Cell (darTreg) Therapy in Liver Transplantation
- Northwestern University[3]
  - Immunoregulatory mechanisms might be amplified in subjects with identical HLA
- Stanford[4]
  - HSCT in conditioned HLA-identical related kidney recipients

1.ClinicalTrials.gov Identifier: NCT01780454; 2.ClinicalTrials.gov Identifier: NCT02188719;
3. ClinicalTrials.gov Identifier:NCT00619528; 4.ClinicalTrials.gov Identifier:NCT00185796

Clinical Connections

- Antibody-mediated injury can be a major determinant of late kidney allograft failure
- Immunosuppression is a delicate balance and the challenge of optimizing treatment is to:
  - Maintain efficacy
  - Prevent DSA
  - Preserve GFR
- Adherence to immunosuppressive therapy remains a problem in transplant medicine
  - Engaging the patient can make a difference

Questions?

How to Collect Credit for This Activity

Complete the Pre-Survey, Credit Request Form and Evaluation Form found on your table.

Please submit your completed forms to conference staff before you leave in order to receive your credit.

Downloadable Resources

- Presentation slides and downloadable resources are available online at **www.CMEOutfitters.com/ATCresources**

Educational Opportunities with CME Outfitters

This activity will be available as a web replay beginning on 7/15/16.

Please visit **www.cmeoutfitters.com** to see a complete list of upcoming, and archived activities that CME Outfitters offers.