The Immunosuppression Balancing Act:

Preserving Long-Term Allograft Function for Optimal Patient Outcomes

May 2, 2017

12:45pm – 1:00pm
Registration
1:00pm – 2:15pm
Symposium

McCormick Place
Convention Center
South Building, #406A
Chicago, IL

Provided by
CME Outfitters

This program is not affiliated with ATC.

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(Moderator)

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Flavio G. Vincenti, MD

Disclosures

- ***Research/Grants:*** Alexion; Astellas Pharma US, Inc.; Bristol-Myers Squibb Company; Genentech, Inc.; Immucor; Novartis Pharmaceuticals Corporation

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John R. Lake, MD

Disclosures

- ***Research/Grants:*** Eisai Inc.; Mallinckrodt Pharmaceuticals; Ocera Therapeutics, Inc.
- ***Speakers Bureau:*** Novartis Pharmaceuticals Corporation
- ***Consultant:*** Novartis Pharmaceuticals Corporation; Vital Therapies, Inc.

Learning Objective 1

Monitor levels of immunosuppression in transplant recipients & at least every three months to document success & long-term survival.

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Learning Objective 2

Assess for DSA HLA antibodies to prevent AMR in kidney & liver transplants.

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Learning Objective 3

Develop a long-term strategy to promote medication adherence through patient engagement & education.

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Preserving Long-Term Allograft Function

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Major Risk Factors That Impact Allograft Failure

- Laissez-Faire Immunosuppression (under/over) ➔ greater vigilance required
- DSA ➔ post-treatment monitoring and intervention
- Subclinical inflammation ➔ in protocol biopsies
- Immunosuppression related toxicities ➔ nephrotoxicity
- Cardiovascular/metabolic complications ➔ more aggressive diagnosis and treatment of NODAT and hypertension
- Nonadherence ➔ require predictive metrics and better patient education

Preserving Long-Term Allograft Function

- Prevent and treat donor-specific antibodies (DSA) and antibody-mediated rejection (AMR)
- Understand the pathogenesis of inflammation and fibrosis and treat it
- Alter approach to renal preservation
  - Calcineurin inhibitor (CNI) minimization is not the answer
    - Conversion to mTORi should be selective and potential risk of new DSA should be considered
    - Low dose CNI with mTORi results in about 5 ml/min of preserved GFR[1]
  - Novel Therapies
    - Belatacept costimulation
    - Anti-CD40?
- Apply Precision Medicine to transplantation

mTORi = Mammalian target of rapamycin inhibitor; GFR = Glomerular filtration rate

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

Optimizing and Monitoring Immunosuppression

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Case #1

- 19-year-old male, living donor kidney transplant at age 13
- Care transferred to University medical center
- Reports that he is adherent to medication, and uses smartphone apps, alarms, text reminders
- Patient missed several lab tests and doesn’t know what his creatinine levels are
- Immunosuppressant level below normal

Audience Response

Following lab tests, his creatinine is 1.4 mg/dL. His typical range is 1.1 mg/dL-1.3 mg/dL.

What is your next best step?

A. Adjust immunosuppressant dose
B. Admit to hospital for kidney biopsy
C. Probe further to confirm that he is adherent to his medication
D. Order biomarker test

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

- With current treatment regimens, a relatively high proportion of transplant recipients experience under-immunosuppression or over-immunosuppression
- 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

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

The Goal of Optimizing Immunosuppression

- Maintaining efficacy
- Preventing DSA
- Preserving GFR

Rear View Mirror Strategies Do Not Work

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CLINICAL RESEARCH www.jasn.org

Adverse Outcomes of Tacrolimus Withdrawal in Immune–Quiescent Kidney Transplant Recipients

Donald E. Hricik,* Richard N. Formica,† Peter Nickerson,‡ David Rush,‡ Robert L. Fairchild,§ Emilio D. Poggio,§ Ian W. Gibson,‡ Chris Wiebe,‡ Kathryn Tinckam,‖ Suphamai Bunnapradist,¶ Milagros Samaniego-Picota,** Daniel C. Brennan,†† Bernd Schröppel,‡‡ Osama Gaber,§§‖‖ Brian Armstrong,¶¶ David Ikle,¶¶ Helena Diop,*** Nancy D. Bridges,*** and Peter S. Heeger,‡‡ for the Clinical Trials in Organ Transplantation-09 Consortium

Hricik DE, et al. *J Am Soc Nephrol.* 2015;26(12):3114-3122.

Methods

- The Clinical Trials in Organ Transplantation-09 CTOT Trial
- Randomized, prospective study of non sensitized primary recipients of living donor kidney transplants
- Subjects received rabbit anti-lymphocyte globulin, tacrolimus, mycophenolate mofetil, and prednisone
- 6 months post-transplantation, subjects without *de novo* DSAs, acute rejection (AR), or inflammation at protocol biopsy were randomized to wean off or remain on tacrolimus (TAC)

Hricik DE, et al. *J Am Soc Nephrol.* 2015;26(12):3114-3122.

Results

- Study was terminated prematurely because of unacceptable rates of AR (4 of 14) and/or *de novo* DSAs (5 of 14) in the TAC withdrawal arm

Hricik DE, et al. *J Am Soc Nephrol.* 2015;26(12):3114-3122.

Conclusions

….past performance does not predict future results in manipulating immunosuppresion regimens. Safe and effective application of novel regimens or drug elimination require reliable biomarkers.

The Need for Biomarkers to Optimize and Guide Immunosuppression Therapy

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Lack of Biomarkers and Precision Medicine Has Halted Development of Several Promising Drugs

- Sotrastaurin – a CNI alternative targeting protein kinase C (PKC)
- Alefacept – targeting memory cells
- ASKP1240 – inhibits the CD40-CD154 pathway

Personalized Medicine Isn’t Precision Medicine

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Personalized/Individualized Medicine vs. Precision Medicine

- Personalized medicine has been practiced in transplantation (i.e. low risk vs. high risk)
- Precision medicine requires new diagnostics or biomarkers to select or modify immunosuppression regimens preferable with novel therapies

Biomarkers and Belatacept

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Belatacept-Based CNI Free Immunosuppression

The NEW ENGLAND JOURNAL of MEDICINE

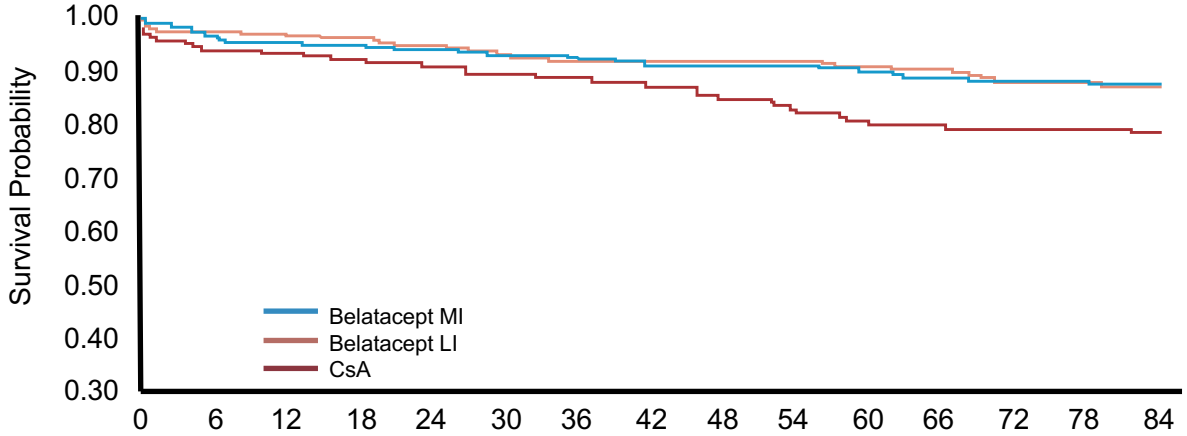
ORIGINAL ARTICLE

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

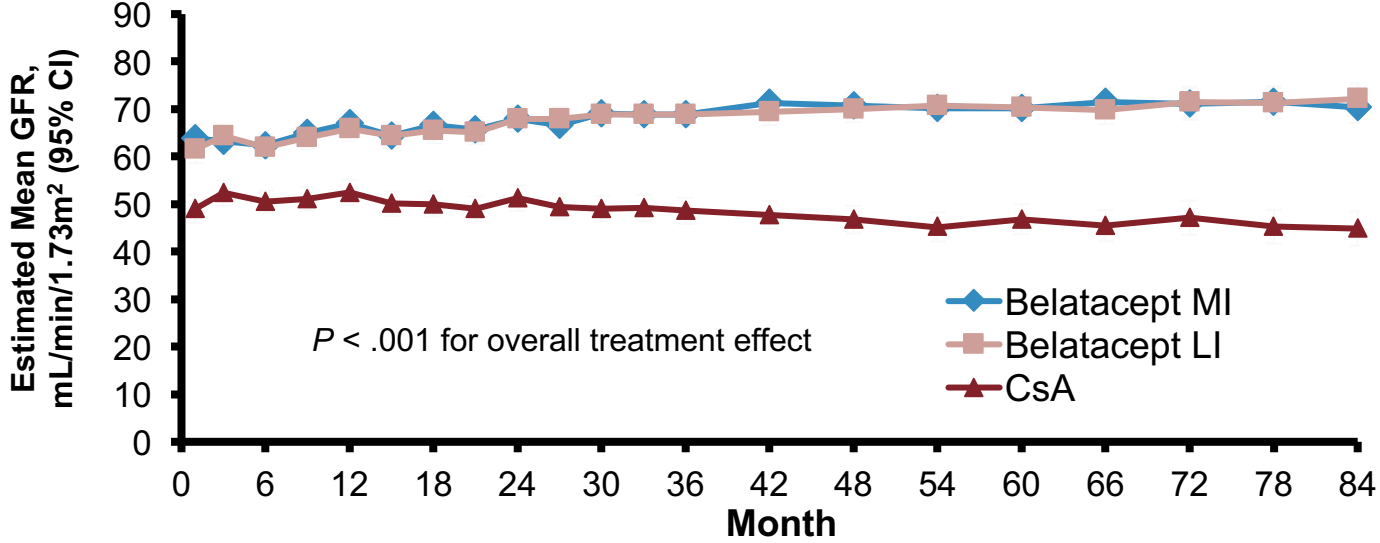
Month 60		
	P - value	HR (95% CI)
Bela MI vs. CsA	0.0100	0.521 (0.306, 0.889)
Bela LI vs. CsA	0.0045	0.477 (0.277, 0.819)

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.

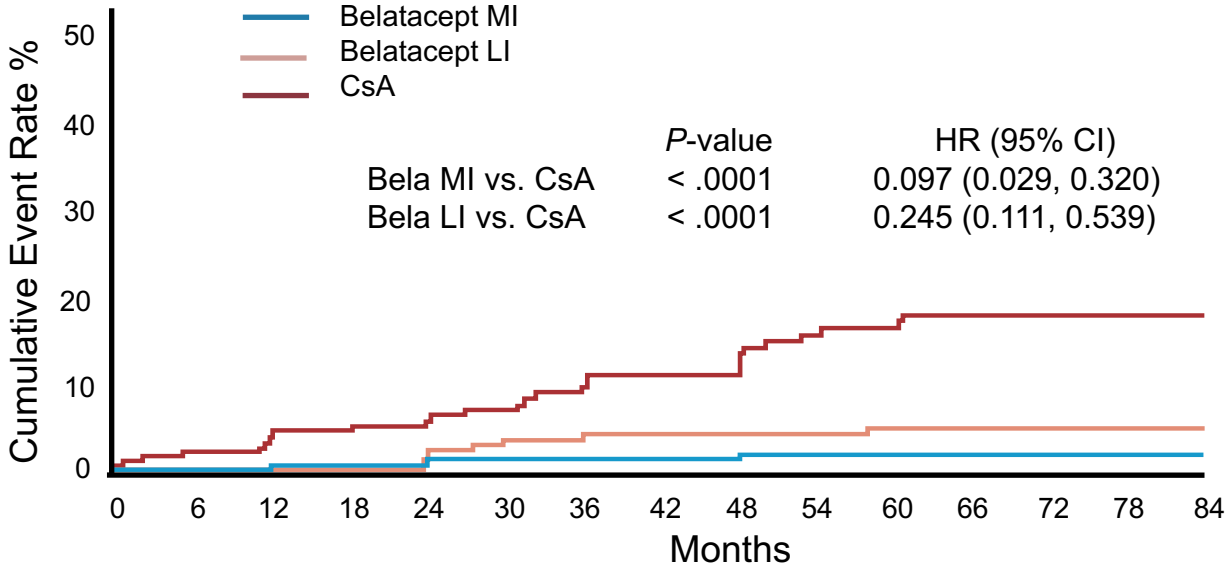
Estimated Mean GFR Over 84 Months: MEM Without Imputation



	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

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

Kaplan-Meier Analysis of Cumulative *De Novo* DSA Over Time



	P-value	HR (95% CI)
Bela MI vs. CsA	< .0001	0.097 (0.029, 0.320)
Bela LI vs. CsA	< .0001	0.245 (0.111, 0.539)

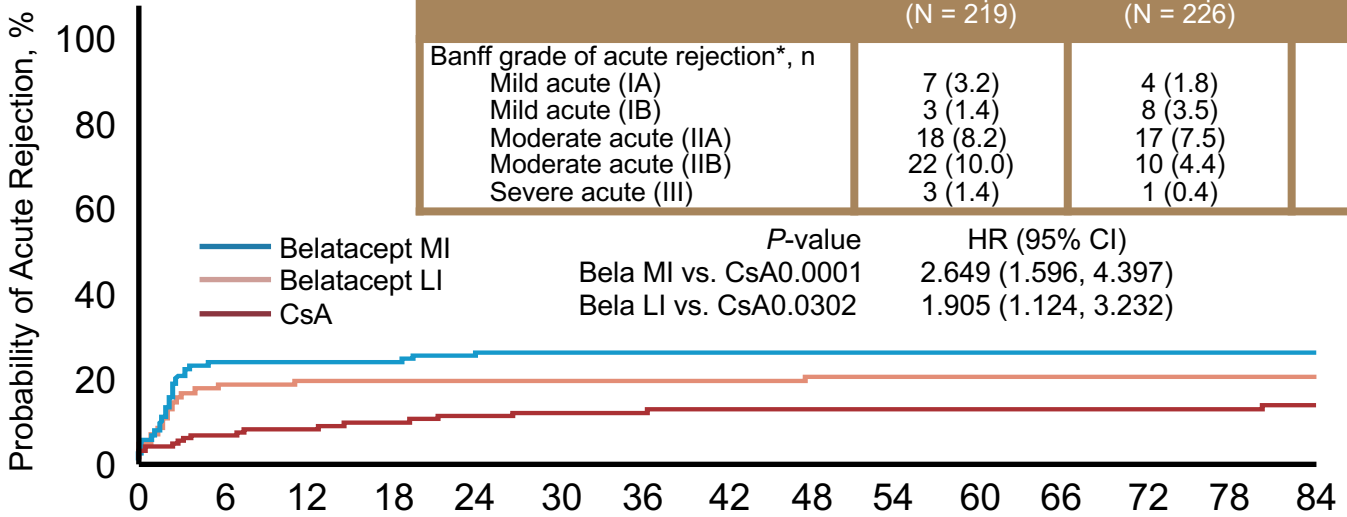
N at risk

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

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

Belatacept Should Be the Prototype Drug to Apply Precision Medicine in Transplantation

- Select patients most likely to respond to costimulation blockade
- Use biomarkers to guide therapy

American Journal of Transplantation 2016; XX: 1–11
Wiley Periodicals Inc.

doi: 10.1111/ajt.13613

CD57+ CD4 T Cells Underlie Belatacept-Resistant Allograft Rejection

J. Espinosa[1,2], F. Herr[3], G. Tharp[4], S. Bosinger[4], M. Song[1], A. B. Farris III[5], R. George[1], J. Cheeseman[1,2], L. Stempora[1,2], R. Townsend[6], A. Durrbach[3,7] and A. D. Kirk[1,2,*]

Received 24 July 2015, revised 16 October 2015 and accepted for publication 18 October 2015

Espinosa J, et al. *Am J Transplant*. 2016;16(4):1102-1112.

kSORT (Kidney Solid Organ Response Test) Rejection

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

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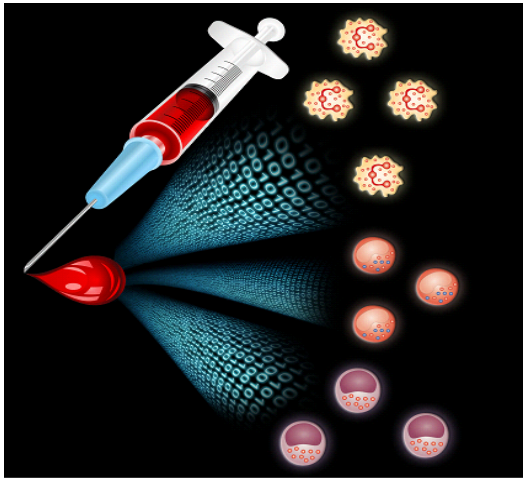
kSORT
Kidney Solid Organ Response Test

The answer in a drop of blood…..

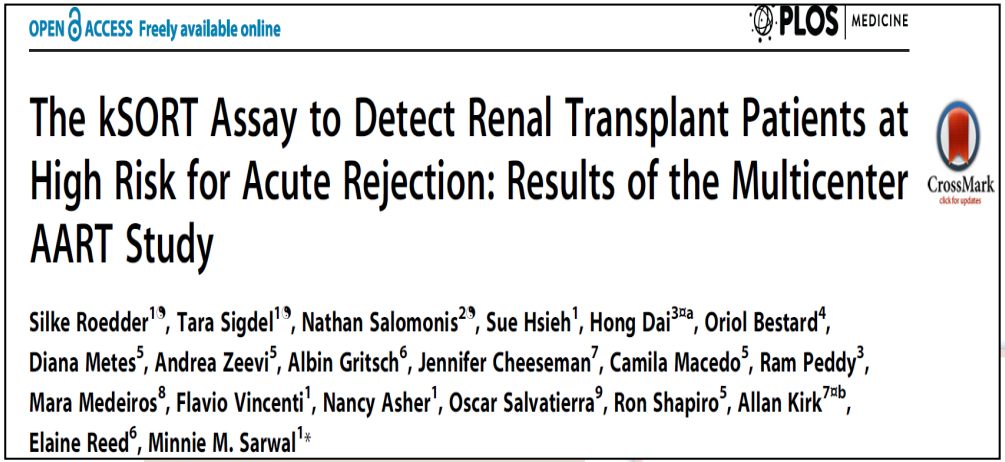
17 gene PCR test measuring graft immune activation by RNA isolated from whole blood



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.

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*]

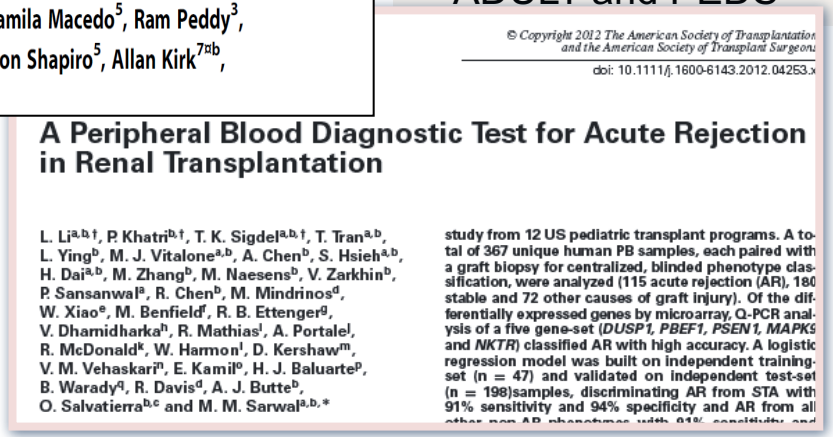
N = 558 biopsy matched blood samples profiled by QPCR

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

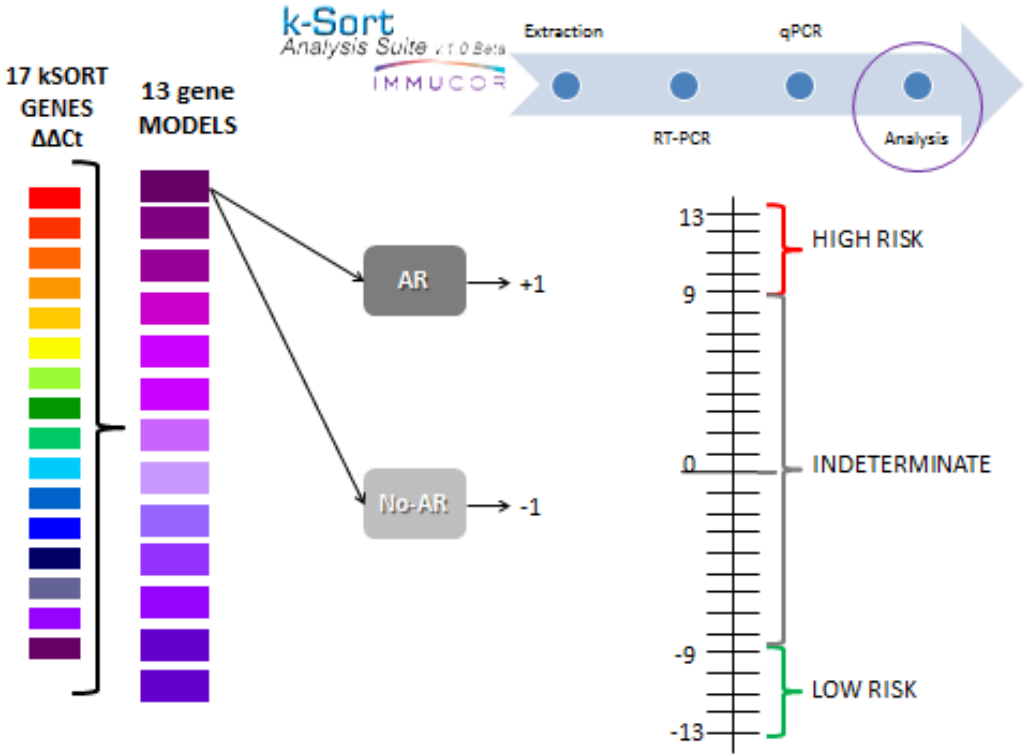
A Peripheral Blood Diagnostic Test for Acute Rejection in Renal Transplantation

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[j], R. McDonald[k], W. Harmon[l], D. Kershaw[m], V. M. Vehaskari[n], E. Kamil[o], H. J. Baluarte[p], B. Waradi[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.

K-SORT Analysis



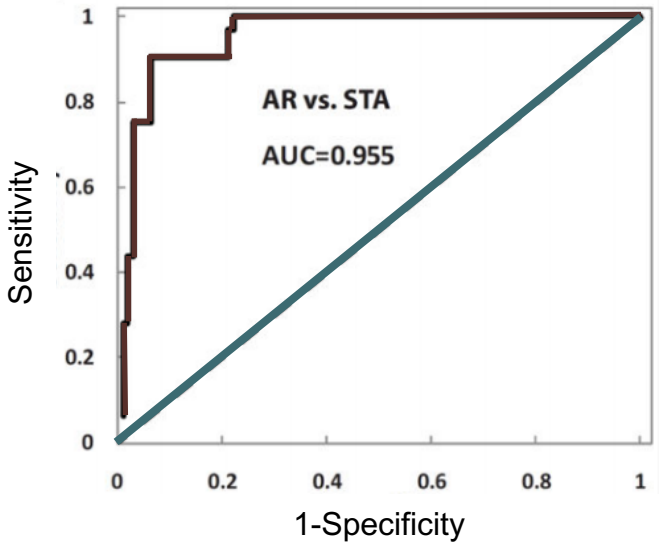
Roedder S, et al. *PLoS Med*. 2014;11(11):e1001759; Li L, et al. *Am J Transplant*. 2012;12(10):2710-2718.

QPCR Validation: SNSO1 NIH Clinical Trial

- PCR validation study, n = 81, 10 genes, pediatric transplant recipients only
- Single center (Stanford University) for initial validation studies and gene selection
- N = 367 unique blood samples matched with renal allograft biopsies, central read (R. Sibley, Stanford)
- Blinded analysis by Rho/NIH

Test performance characteristics

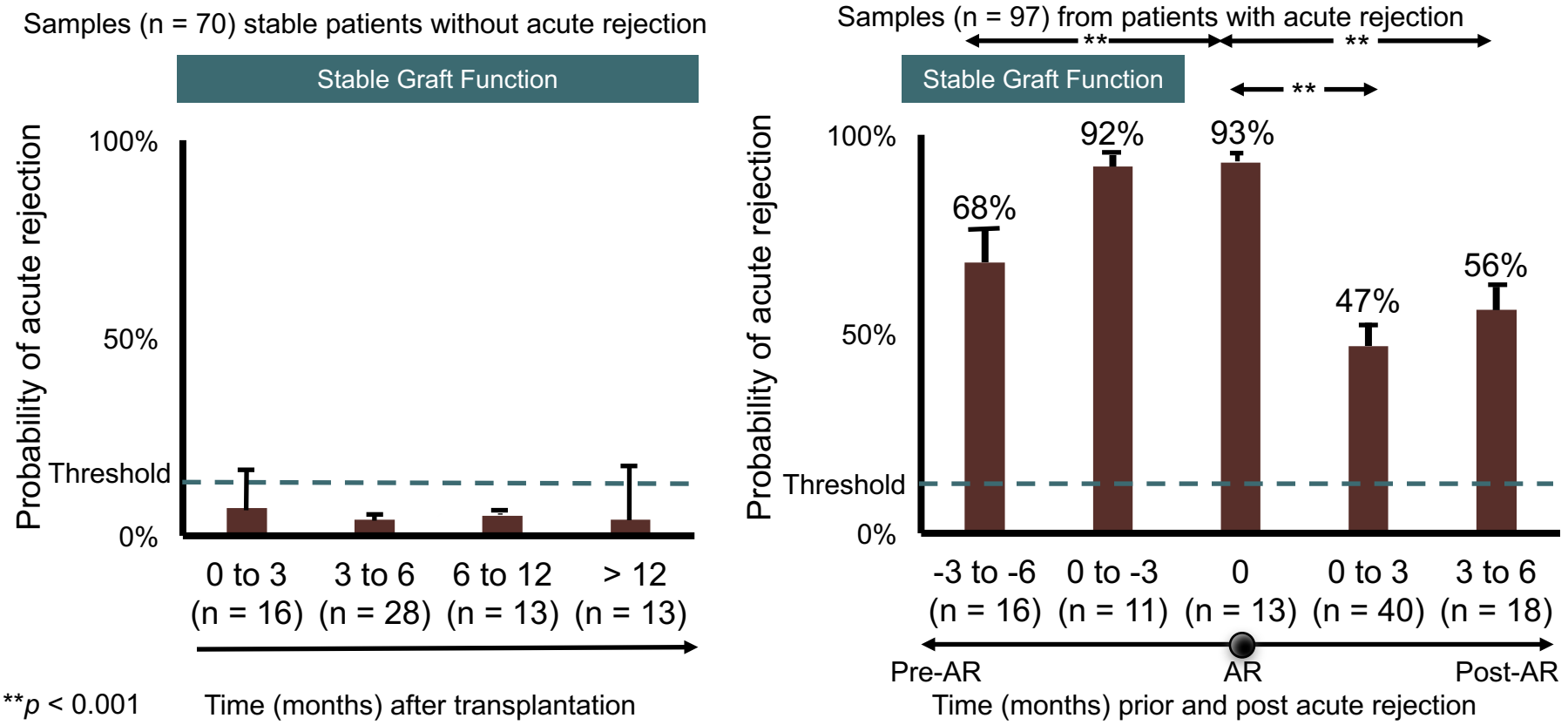
Sensitivity	91%
Specificity	94%
PPV	83%
NPV	97%
AUC	0.9555



QPCR = Quantitative polymerase chain reaction; PCR = Polymerase chain reaction; AR = Allograft rejection; STA = Stable; AUC = Area under the curve; PPV = Positive predictive value; NPV = Negative predictive value

Li L, et al. *Am J Transplant*. 2012;12(10):2710-2718.

kSORT for Prediction of pre-AR



**$p < 0.001$

Li L, et al. *Am J Transplant*. 2012;12(10):2710-2718.

Learning Objective 2

Assess for DSA HLA antibodies to prevent AMR in kidney & liver transplants.

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Current Status of Desensitization and AMR

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Desensitization: Unmet Needs

- Patients with high cPRA on the deceased waiting list
- Patients with DSA to their living kidney donors

Desensitization of Highly Sensitized Patients or Recipients with DSA

- Very few transplant centers are actively desensitizing patients
- Current regimens consist of IVIg + Rituximab ± plasmapheresis
- Outcome still problematic because of risk of AMR, cAMR, and risks of over-immunosuppression
  - A major concern is being cited by CMS for poor outcome and placed on probation (DSA not a mitigating factor)

The Importance of Preventing AMR and Post-Transplant DSA

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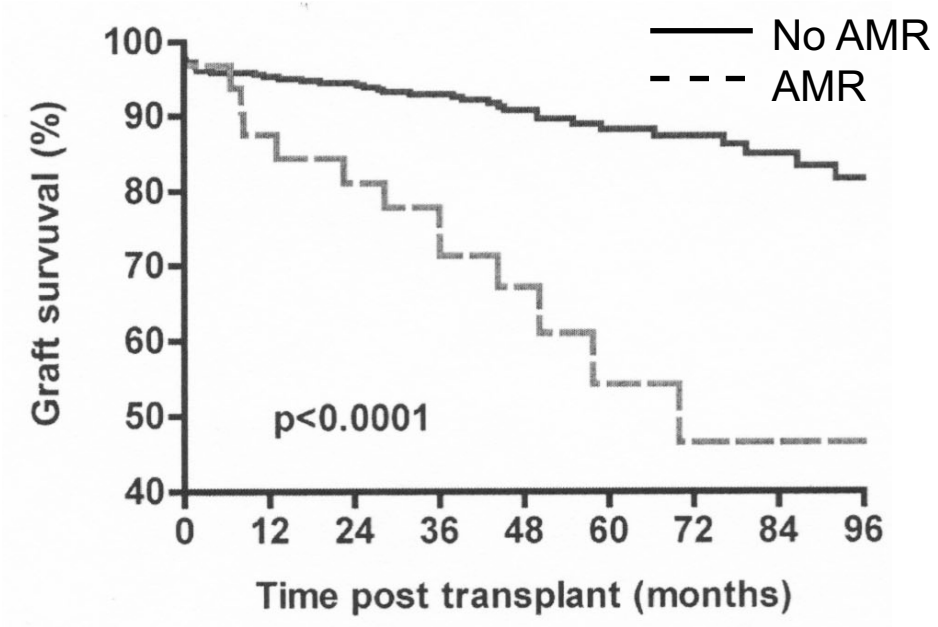
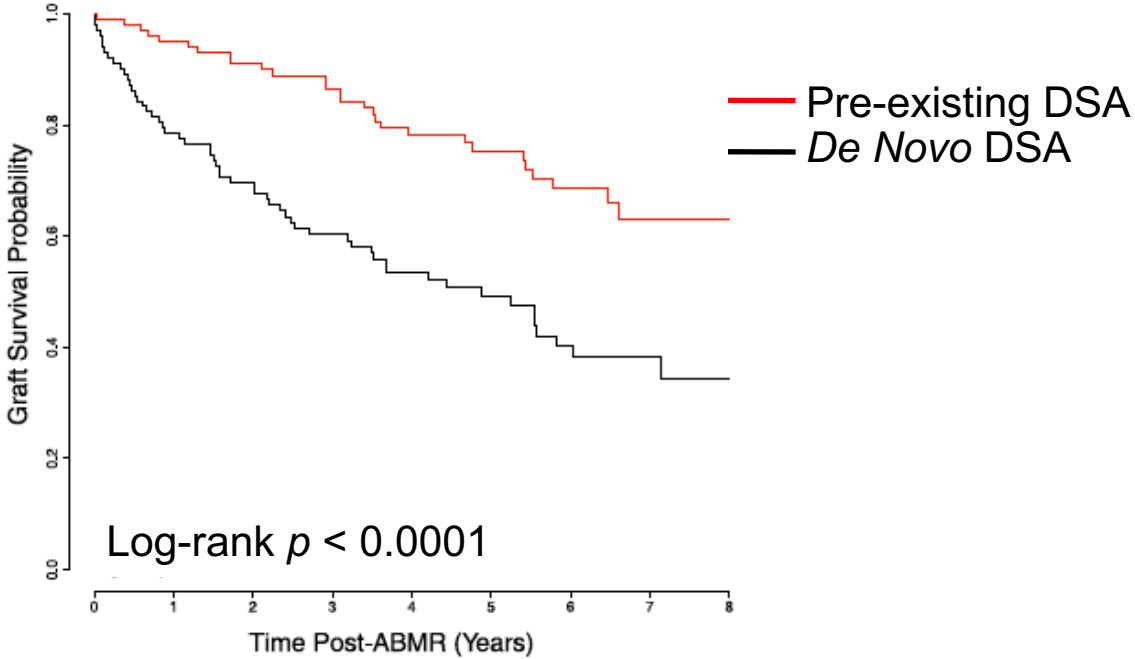
Graft Survivals of Those With and Without Episodes of Acute Antibody-Mediated Rejection



Number at Risk									
Month	0	12	24	36	48	60	72	84	96
No AMR	370	338	323	256	172	121	89	61	41
AMR	32	29	26	24	12	9	7	6	4

Lefaucheur C, et al. *J Am Soc Nephrol*. 2010;21:1398-1406.

AMR Due to Preexisting vs. *De Novo* DSA in Kidney Allograft Recipients



Number at Risk									
Year	0	1	2	3	4	5	6	7	8
Pre-existing DSA	103	95	87	74	61	49	32	17	11
De novo DSA	102	80	70	56	43	31	22	10	4

N = 771 kidney biopsy specimens

Aubert O, et al. *J Am Soc Nephrol*. 2017 Mar 2. doi: 10.1681/ASN.2016070797. [Epub ahead of print].

Why Do Grafts Fail Long-Term?

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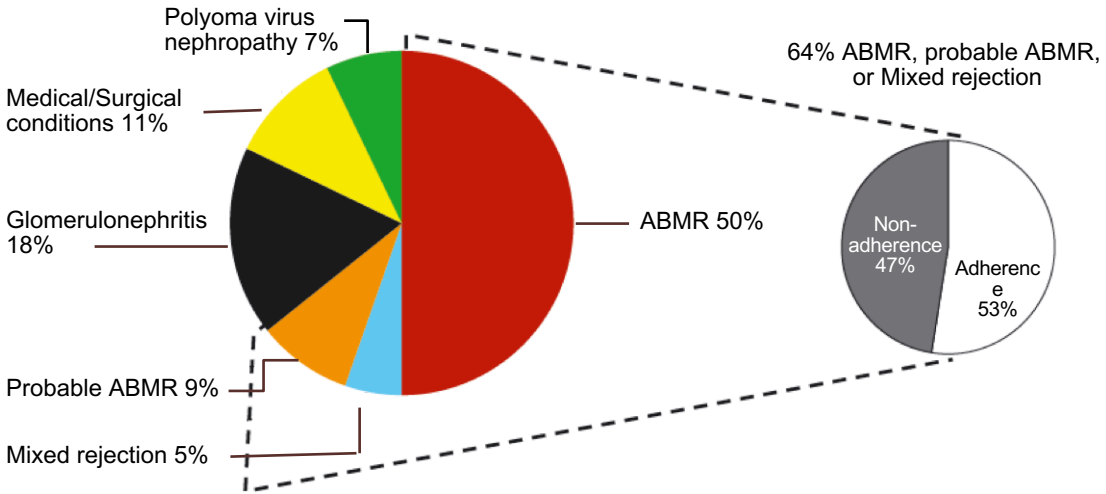
The Role of AMR and Nonadherence in Kidney Transplant

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



N = 315

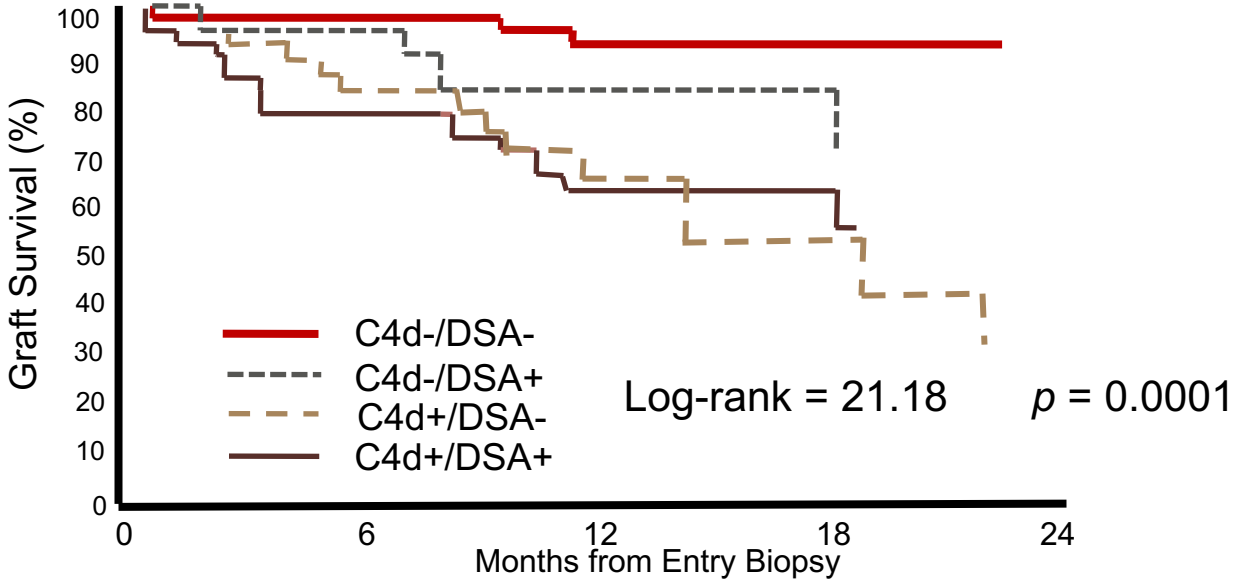
Sellarés J, et al. *Am J Transplant*. 2012;12(2):388-399.

[290] C4d (+) and Donor Specific Antibody (DSA) Have Differential Impact on Outcome after Late Renal Allograft Biopsy

Robert Gaston, A. Fieberg, R. Leduc, J. Connett, F. Cosio, S. Gourishankar, J. Grande, P. Halloran, L. Hunsicker, B. Kasiske, A. Matas, D. Rush, J.M. Cecka

Am J Transplant. 2009;9:274-275

DeKAF Study Graft Survival by C4d/DSA Group
Long-Term Cohort Entry Biopsies



	6	12	18	24
C4d-/DSA- :56	48	33	12	7
C4d-/DSA+ :25	19	13	8	5
C4d+/DSA- :29	21	16	9	6
C4d+/DSA+ :34	22	13	6	3

Gaston R, et al. *Am J Transplant.* 2009;9:274-275.

Summary

- To improve long-term outcomes we need novel immunosuppressive agent that suppress both T-cells and B-cells
- Will require that novel agents preserve renal function

Is the Approach to Allograft Function Different for Liver Transplants?

Can experiences from kidney transplantation inform liver transplantation?

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Case #2

- 34-year-old male, positive for HCV and MPGN
- Creatinine: 2.2 mg/dL
- Proteinuria: 2.5 gm/mg creatinine
- Urinalysis: 10-15 RBC
- Cryoglobulins positive
- Esophageal varices
- MELD score = 20

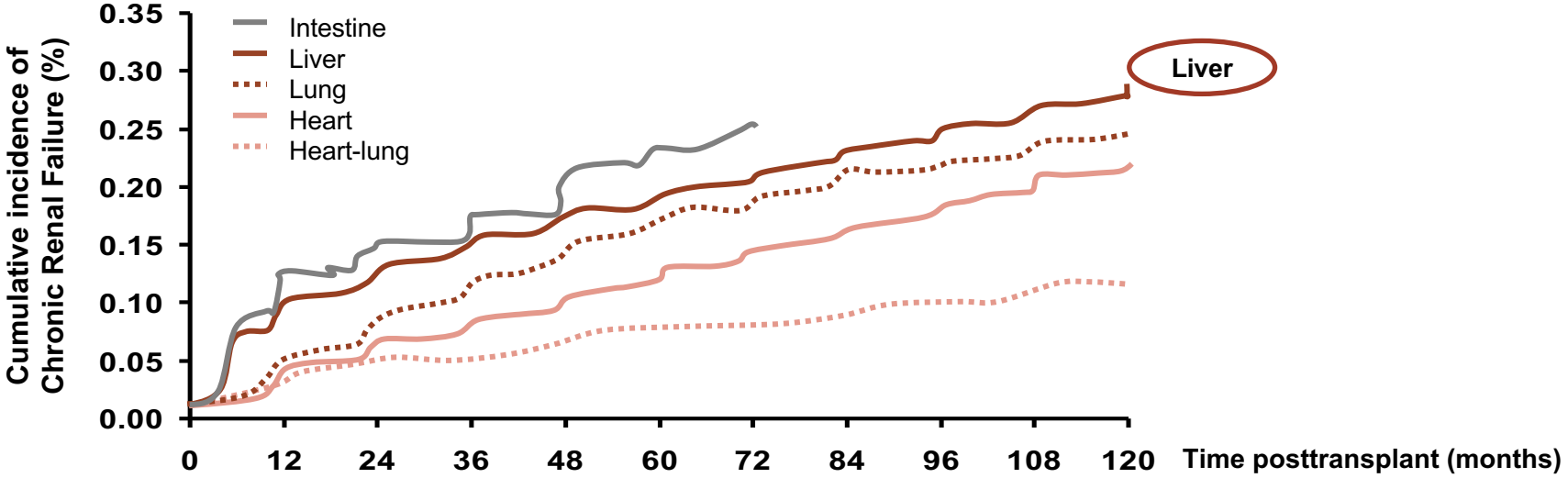
HCV = Hepatitis C virus; MPGN = Membranoproliferative glomerulonephritis; RBC = Red blood cells; MELD = Model for end-stage liver disease

Cast #2 Continued

- 98% cPRA positive
- Has several class I DSA, over MFI 7500
- One class II DSA, over MFI 15,000

cPRA = Panel reactive antibody; MFI = Mean fluorescence intensity

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

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

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

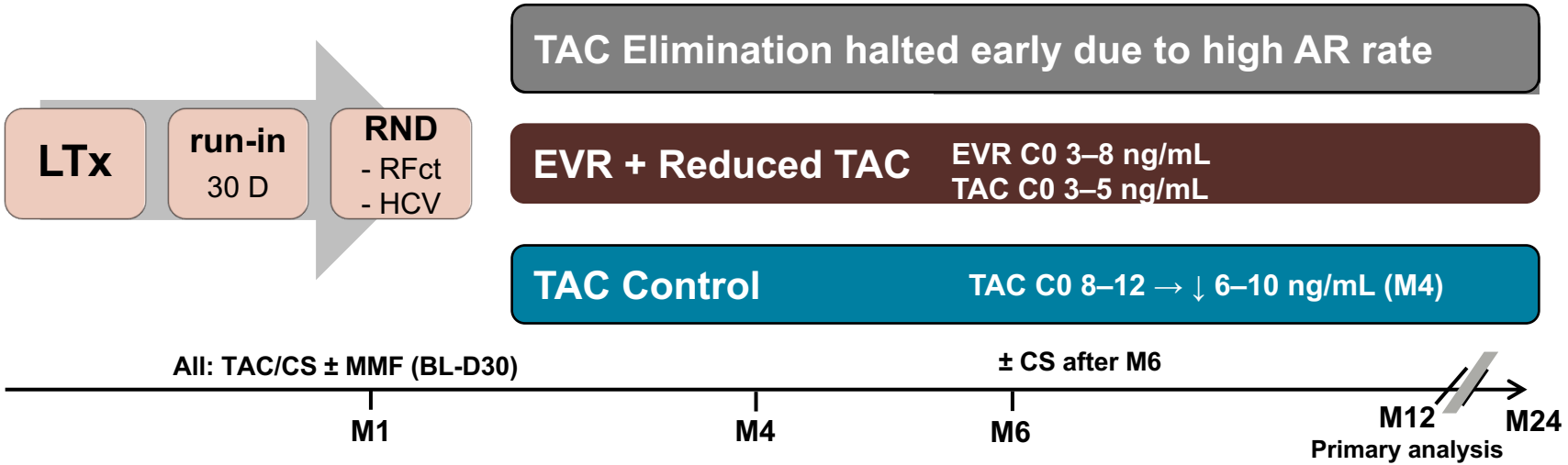
Renal function by stage of kidney disease in liver transplant patients (n = 1502)

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.

H2304: Study Design

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

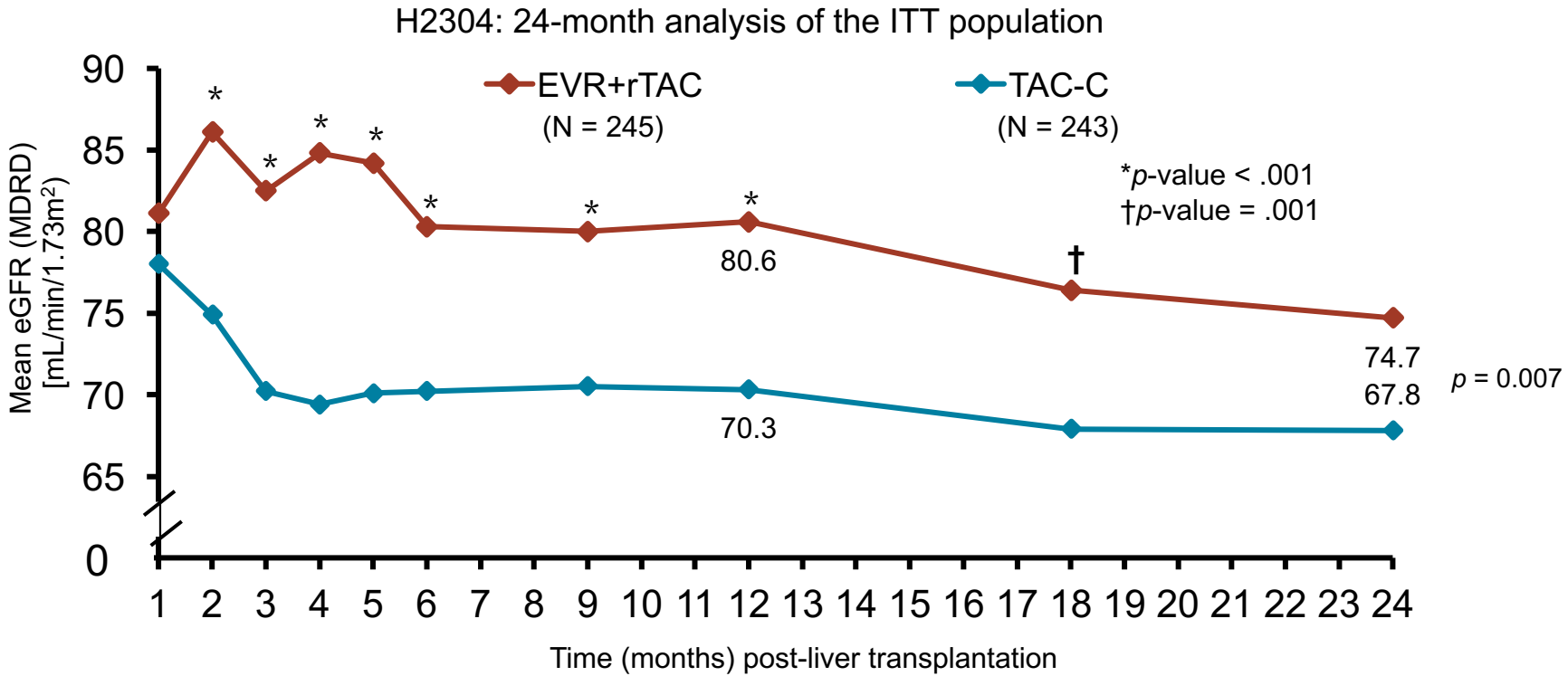


Enrollment into TAC-WD arm was stopped due to higher rejection rates and protocol was amended based on DMC recommendation (Apr 2010)

BL = baseline; C0 = concentration; CS = corticosteroids; d = day; EVR = everolimus; HCV = hepatitis C virus; M = month; LTx = liver transplantation; RND = randomization; RFct = renal function;

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.

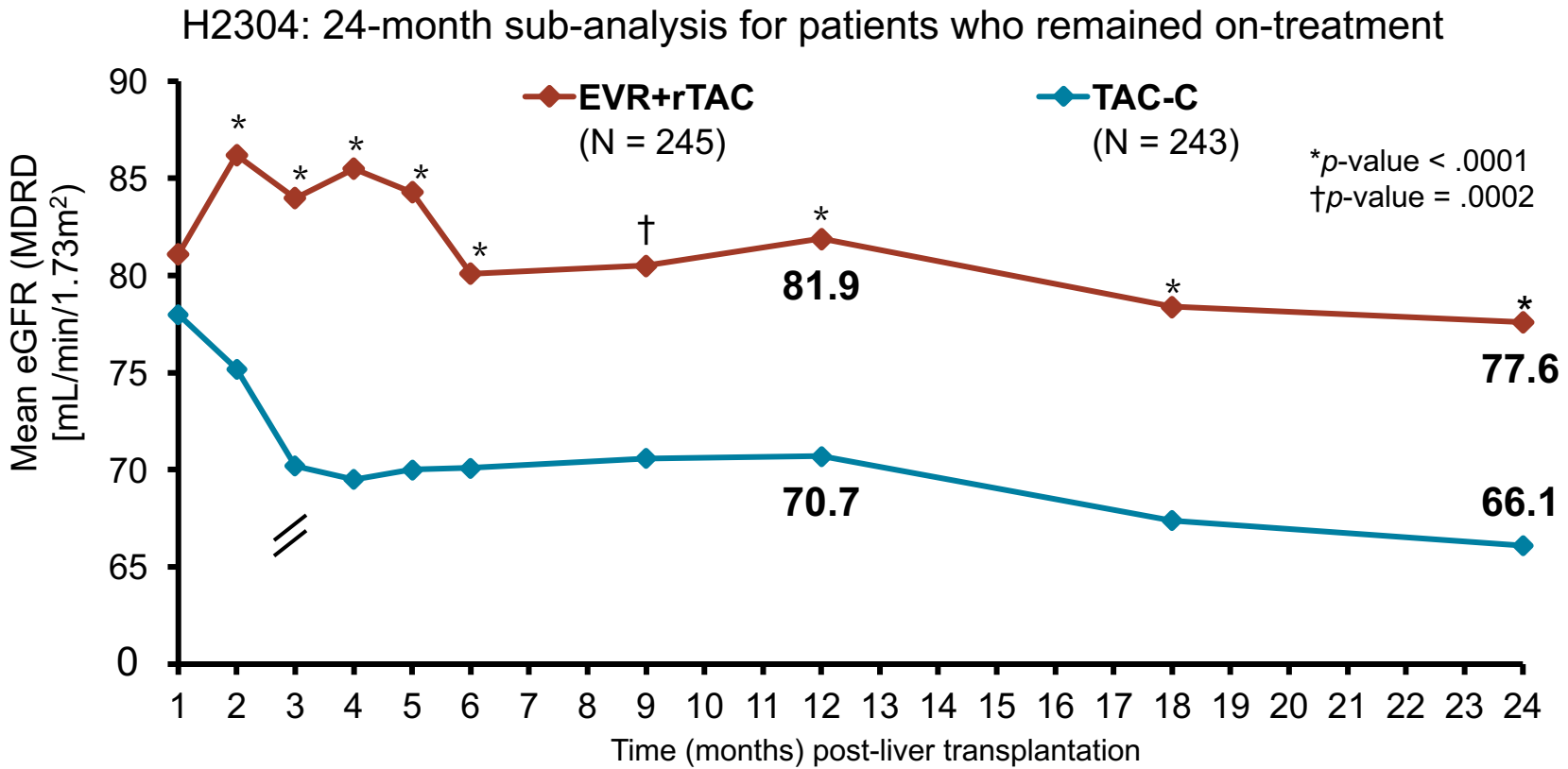
Significantly Better Renal Function with EVR + rTAC vs TAC-C is Observed 2 Months After Transplantation and Sustained Until 24 Months



eGFR = estimated glomerular filtration rate; ITT = intent-to-treat; MDRD = Modification of Diet in Renal Disease;

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

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



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

What About AMR in Liver Transplants?

Do Donor Specific Antibodies Influence Outcomes?

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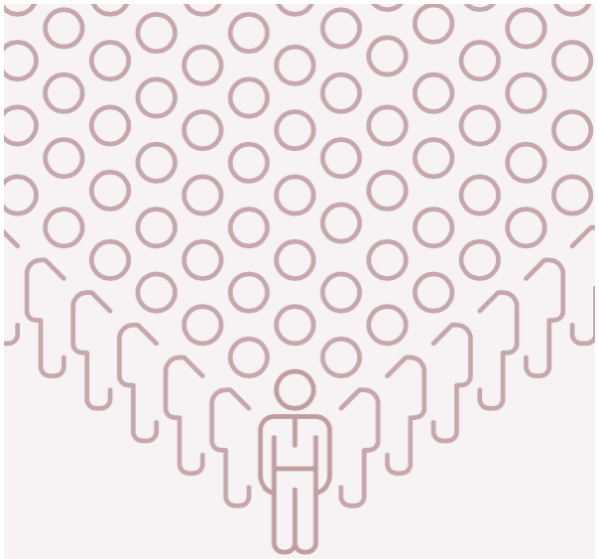
Historically Speaking….

- Hyperacute rejection is phenomenally rare after liver transplantation
- Successful liver transplants observed in highly sensitized patients
- Large, retrospective studies found no association with adverse outcomes
- Widely held view emerged that AMR was not a problem in liver

Unexplained Graft Loss…AMR?



60 patients with early unexplained graft loss

- 53% had preformed DSAs
- 54 patients had no evidence of AMR
- 3 incomplete, 3 classical AMR
- Movement of pendulum to recognition as a cause of graft loss

O'Leary JG, et al. *Liver Transpl*. 2014;20(2):218-227.

Antibody Mediated Rejection

- Unusual but increasingly recognized cause of graft failure
- Donor-specific antibodies – Class II with MFI >10,000
- Compatible histology
- Positive C4d staining

O'Leary JG, et al. *Am J Transplant*. 2014;14(4):779-87.

DSAs and Outcomes in First Year

- 90 consecutive patients including 20 with DSAs
- 12 class I, 5 class II and 3 both I and II
- 90% reduction by day 7
- No difference in acute cellular rejection (45% and 31%)
- No difference in liver function or survival after week 1

Taner T, et al. *Am J Transplant.* 2012;12(6):1504-1510.

Histological Features

- Portal microvascular endothelial cell enlargement involving portal tracts with sparse microvasculitis defined by
  - 3-4 marginated and/or intraluminal monocytes, neutrophils, or eosinophils in the maximally involved capillary with generally mild dilation
- Monocytic, esosinophilic, or neutrophilic microvasculitis/ capillaritis defined as
  - At least 5-10 leukocytes marginated and/or intraluminal in the maximally involved capillary prominent portal and/or sinusoidal microvasuclar endothelial cell enlargement
- Marked capillary dilatation, microvascular inflammation, at least focal microvascular disruption with fibrin deposition, extravasation of RBCs in portal stoma and/or space of Disse

Demetrius AJ, et al. *Am J Transplant*. 2016;16:2816-2835.

The Role of DSA HLA Alloantibodies in Liver Transplantation: Facts and Possibilities

Facts

- AMR occurs in liver allografts
- The liver does not completely protect the kidney
- Sensitivity and specificity of DSA testing variable

Possibilities

- Only some DSA lead to pathological outcomes
- Do DSAs act as co-factors or synergizers?
- DSA may cause or accelerate fibrosis progression
- Cellular memory may play a role in outcome
- DSAs may have a role in plasma cell hepatitis
- DSAs may have a role in resistant rejection or chronic rejection

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

The Role of DSA HLA Alloantibodies in Liver Transplantation: Opportunities

- Help define the pathological criteria for AMR
- Work to replacing or improving C4d staining in diagnostics
- Characterize the molecular signature of AMR
- Develop monitoring schedule post-transplant
- Characterise who will benefit from altered immunosuppression
- Determine who should be treated for AMR
- Inform long-term view AMR and graft survival
- Design AMR treatment trials

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

Learning Objective 3

Develop a long-term strategy to promote medication adherence through patient engagement & education.

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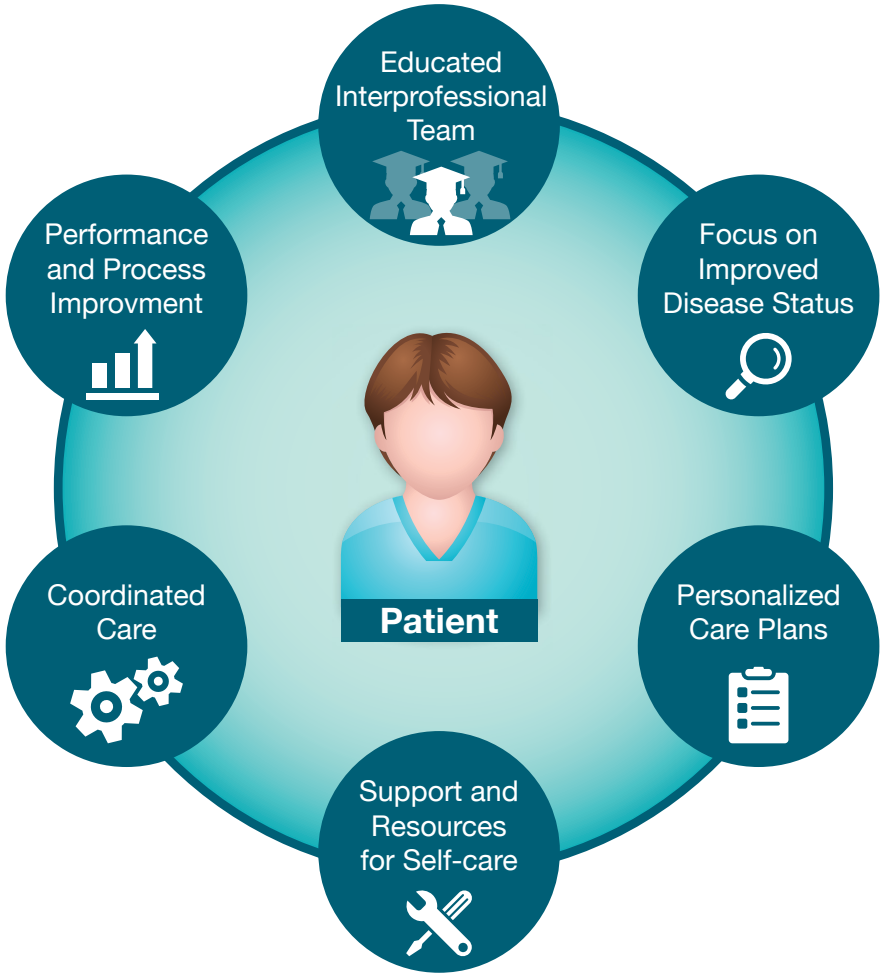
Engaging Patients as Partners

Audio

- Thinking about discussions within your online organ transplant community, do transplant patients feel as though they are active participants in their treatment strategy and that their opinions are valued by the clinicians they see?
  - I didn't really feel like I was very active in my treatment or anything. Doctors just kind of said this is what is going to happen. I do believe a lot of people who I've talked to online have said similar things. They've said they wished they would have explained things more to them.

Patient-Centric Approaches to Improving Medication Adherence



Engaging Patients as Partners

- Thinking about discussions within your online transplant community, would they say that they feel well-informed by their transplant aftercare clinicians about the need to take their medications and monitor their treatment regularly?
  - There were a lot of patients, I've been really surprised, who don't even know what this or that medication does, or why they're taking it, or the importance of doing that. I think it really does depend on the center, the quality of the center, and the physicians
  - I think most of them feel that they are getting adequate direction, instruction, whatever from their clinicians. It's well explained for most of the people in our community, however it's the follow-through at the patient level that seems to give the biggest problem.

Motivations, Challenges, and Attitudes to Self-Management

- 50 studies of 1,238 kidney transplant patients identified motivations and challenges to self-management
  - Empowerment through autonomy, adaptive coping
  - Prevailing fear of consequences
  - Burdensome treatment, inadvertent forgetfulness
  - Social accountability, gratitude toward donor, medical team
- Multicomponent interventions incorporating personalized care planning, education, psychosocial support, decision aids, and self-monitoring tools may foster self-management capacity and improve transplant outcomes

Jamieson NJ, et al. *Am J Kidney Dis*. 2016;67(3):461-478.

Improved Adherence via Mobile Technology

- 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

Engaging Patients as Partners

- Do transplant aftercare clinicians typically discuss with patients the need to monitor for problems such as antibody mediated rejection or other possible causes of organ failure?
  - I don't think generally patients, transplant recipients, are very knowledgeable about things such as antibody-mediated rejection. These are not things that they are told about. They are certainly told about quote-unquote organ failure, but I don't think that they are informed about specifics of those things that occur, or could occur post-transplant.
  - Even in my involvement in the transplant community, I couldn't say that I am even feel as educated about what problems such as those would look like or what symptoms would be apparent so that you could alert, of course, yourself, but a family member or someone, or your doctor.

Strategies We Employ

Faculty discussion

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Questions & Answers

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