Key issues in clinical trials in solid organ transplantation

New endpoints for New Generation Clinical Trials: A Summary of Banff proposals

Julio Pascual
Hospital del Mar
Barcelona

Welcome and opening remarks.
History and future of the Banff Classification.
Where the present lesion scoring criteria came from, and the continued need for ease of use and time efficiency

Kim Solez

Originally we had mule deer poking their heads into the meeting rooms.

Now we have complex data requiring artificial intelligence but outcome should be very good for patients. We've come a long way!

Kim Solez

FOLIA HISTOCHEMICA
ET CYTOBIOLOGICA
Vol. 47, No. 3, 2009
pp. 355-361

Review article

AI (artificial intelligence) in histopathology – from image analysis to automated diagnosis

Klaus Kayser[1], Jürgen Görtler[2], Milica Bogovac[1], Aleksandar Bogovac[1], Torsten Goldmann[3], Ekkehard Vollmer[3], Gian Kayser[4]

[1]UICC-TPCC, Institute of Pathology, Charite, Berlin, Germany
[2]DeepComputing, IBM, Antwerpen, Belgium
[3]Department of Pathology, Research Center Borstel, Borstel, Germany
[4]Institute of Pathology, University Freiburg, Freiburg, Germany

"The implementation of a complete connected AI supported system is in its childhood. Application of AI in digital tissue – based diagnosis will allow the pathologists to work as supervisors and no longer as primary "water carriers". Its accurate use will give them the time needed to concentrating on difficult cases for the benefit of their patients."

Optimizing Statistical Methods for Generating Robust Endpoints

Dorry Segev

Goals for Endpoints

- Clinically relevant
- Highly quantitative / easily diagnosible
- Consistently ascertainable in an unbiased way
- Optimally sensitive to treatment
- Precise
- Early response
- Common

Dorry Segev

FDA Definitions

- A clinical endpoint (CEP) is an outcome or variable representing a measure of how a patient feels, functions or survives.
  In renal transplantation, the gold-standard CEP is patient and graft survival measured at an appropriate time point…infrequent

- A biomarker is an objectively measured characteristic that is evaluated as an indicator of normal biological or pathogenic processes or pharmacologic responses to an intervention. A biomarker may allow for faster, more efficient clinical trials but greatly depends on the quality of data supporting its use and the setting in which applied.

- A surrogate endpoint (SEP) is a biomarker intended to substitute for a CEP and expected to predict clinical benefit.

Dorry Segev

FDA Approval

Prospective RCTs designed to demonstrate superiority of a treatment on a CEP would demand a large sample size and lengthy follow-up.
While the scientific value of such a study would be significant, it would also be expensive and would take years to complete.

A SEP that is 'reasonably likely' to predict a clinical benefit can be used for initial approval. Approval under this regulation requires that the product be studied further after approval to confirm clinical benefit. Extending the pivotal trials which relied on a SEP into the postmarketing period to confirm that the intervention resulted in improved patient and/or graft life, could represent one possible approach.

Dorry Segev

Why use a composite endpoint?

- Statistical efficiency: fewer patients needed
- Underlying biological considerations
- Completeness of drug evaluation
- Information preservation: reduce bias due to informative censoring (e.g. include mortality along with nonfatal events such as rejection, since patients who die may have been at greater risk for rejection)

Dorry Segev

The composite endpoint

- Individual components are all clinically meaningful to the patient
- Hypothesized associations between the intervention and each component are similar
- Correlation between the components is not too high (higher correlation->less efficiency)
- All components should trend in the favored direction
- This is particularly true if some endpoints (e.g. DGF) are much "softer" than others (e.g. mortality) – composite outcome should not be driven only by the "soft" events

Dorry Segev

Goals of Adaptive Strategies

- Increase trial efficiency
- Potentially benefit trial participants
- Reduce cost
- Enhance likelihood of finding a true benefit (if exists)
  - Assign a larger proportion of participants to treatment groups that are performing well
  - Reduce number of participants in treatment groups that are performing poorly
  - Investigate a larger dose range (than nonadaptive designs)
  - Make prospectively planned changes to the future course of an ongoing trial on the basis of an analysis of accumulating data from the trial itself (blinded or unblinded) *without undermining the statistical validity of the conclusions*

Dorry Segev

Adaptive: 2-Stage Design

- Stage 1 is broad dose testing and dose selection by DSMB for stage 2
- *Final analysis can use observations from both stages*
- Requires early (short-term) endpoint
- Requires meticulous planning, operationalization
- Particularly useful when effect size unknown
- No sponsor involvement in dose selection
- Risk of inadequate dose–response modeling
- Detailed simulations before initiation

Dorry Segev

Enrichment Strategies

- (Biomarker-driven) population-enrichment
- Considers treatment effect heterogeneity
- Enrichment Adaptive = (1) study whether a given profile is predictive for success of therapy and (2) enrich population to those most likely to benefit
  - Initially randomize regardless of profile, then interim analysis tests effect modification, and then possibly terminate enrollment for some profiles
  - Final analysis incorporates data from both phases

Dorry Segev

The FDA and Unmet Needs:

The Path to New Therapy for Transplant Recipients

Mark D. Stegall

American Journal of Transplantation 2016; 16: 1094–1101
Wiley Periodicals Inc.

doi: 10.1111/ajt.13582

Personal Viewpoint

Developing New Immunosuppression for the Next Generation of Transplant Recipients: The Path Forward

M. D. Stegall[1,*], R. E. Morris[2], R. R. Alloway[3] and R. B. Mannon[4]

- FDA – 1 year graft and patient survival as an endpoint
- Difficult to improve
- Long-term studies difficult and expensive
- Industry – Views transplantation as a small field, too many reportable complications may tarnish the reputation of a drug used in autoimmunity or other fields
- Transplant Community – fragmented, unable to speak with one voice
- All – belief that current outcomes are great

Mark D. Stegall

The FDA has a long history with poor-performing biomarkers

- No predictive biomarker is approved as a surrogate endpoint for graft loss in transplantation
  - There is a high correlation between the biomarker (ex. acute active antibody mediated rejection per Banff 2013) and subsequent graft loss
  - Biomarker should be “in the pathway of the disease”
  - Too many factors affect eGFR and the correlation between eGFR and graft loss is low

The goal is to identify a predictive biomarker that

- Has a very high correlation with graft loss in the subsequent 1-3 years (ex. >35% fail)
- Represents a process that can either be stabilized or reversed
- Is common enough that a clinical trial can be performed with enrollment in 2 years.

Resolution of Histology as a Biomarker

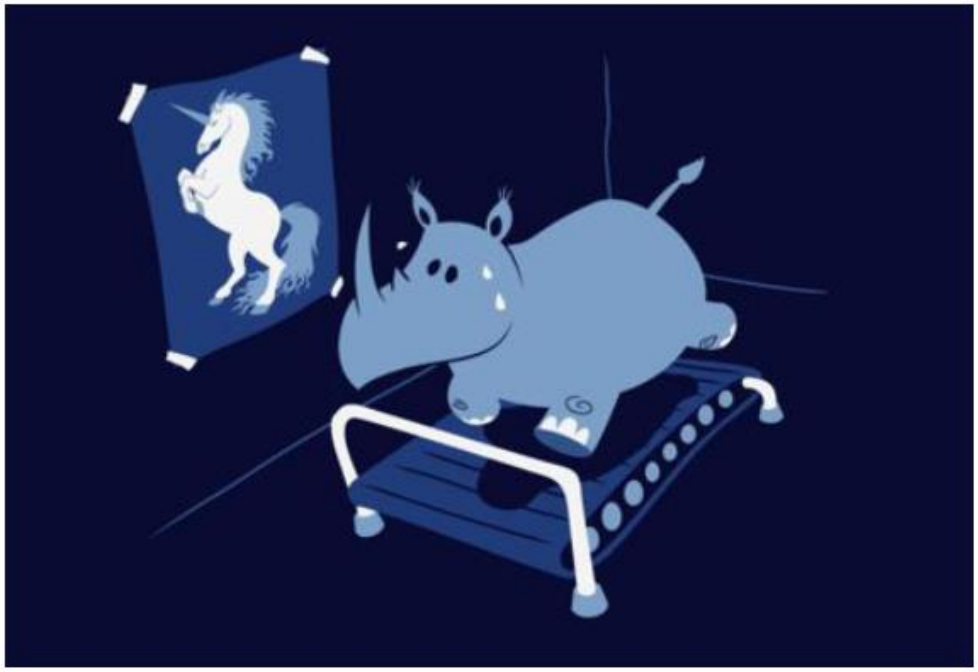
- Histology is the cornerstone of diagnosis and prognosis in nephrology and KT
- Already used by the FDA (precedent)—ex. BPAR in 1st year
- Does not require approval of a new assay (involving other parts of the FDA)
- Will require studies that validate histology as a biomarker
- Might be the pathway to validating other biomarkers.

Mark D. Stegall

DSA monitoring as an end point

Anat R. Tambur

Is that a realistic expectation?



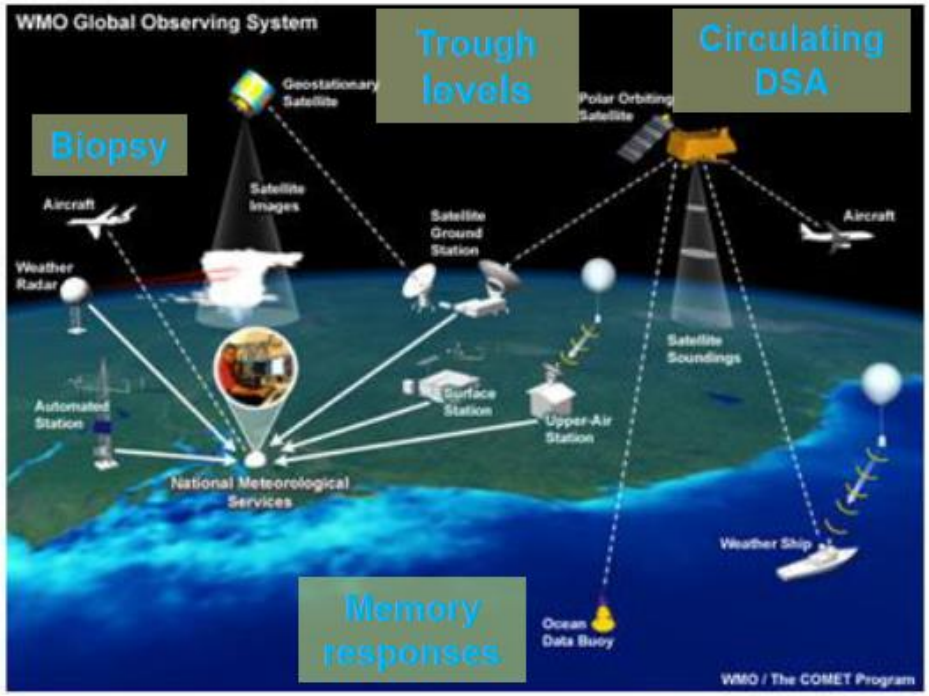
- Testing for DSA pre-transplant and predicting 5-year outcome?
- Monitoring DSA throughout the clinical trial and projecting short-term changes?

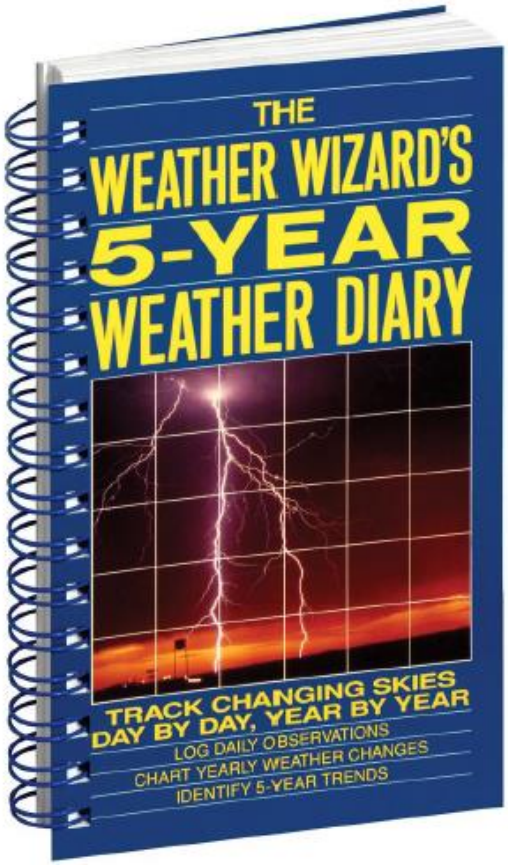
Anat R.Tambur

In Analogy:

Forecasting the weather in 5 years

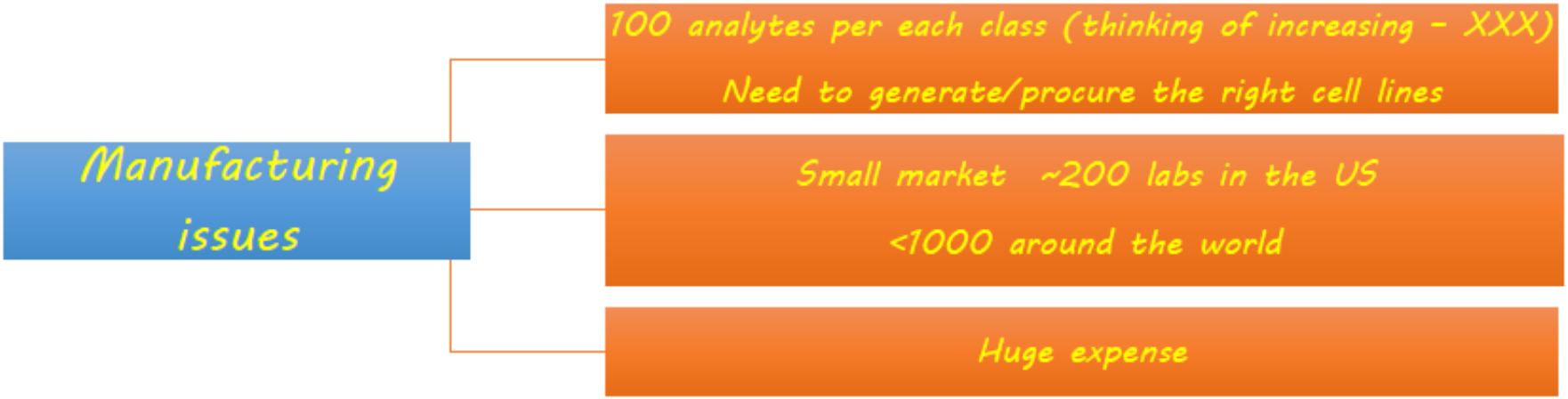
In the Sahara Desert
Versus
In Chicago…





Anat R.Tambur

Why is it not working ?



Anat R.Tambur

New End-Points for New Generation Clinical Trials – DSA?

Make Sure DSAs are Measured Appropriately

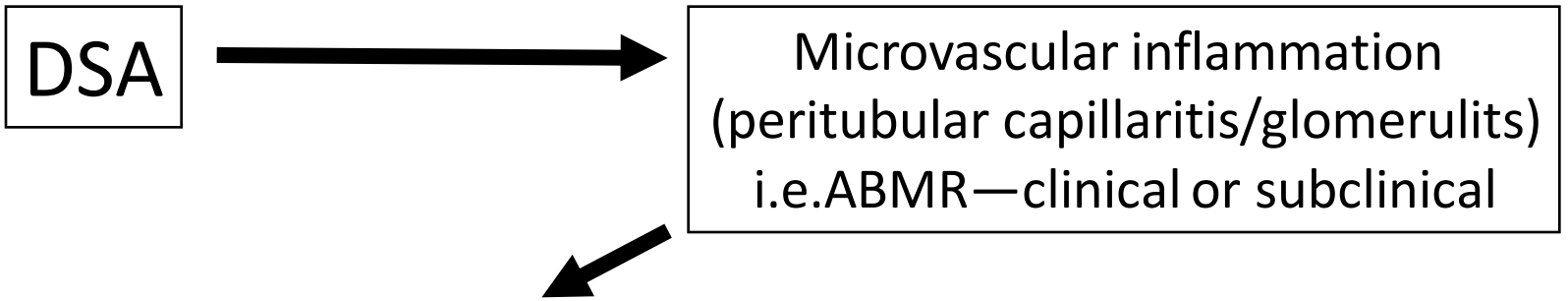
- HR typing of donors (at least "for cause") for all HLA loci
- Assigned Abs based on HR (provided with the kits)
- Determine whether SAB-kit indeed includes reagents to test DSA
- Remove potential inhibitory factors from serum
- Account for potential "Shared-Epitope" reactions
- MFI should not be used as a strict cut-off value
- Monitoring efficacy of treatment is best done by dilution studies

Anat R.Tambur

Potential end points for response to treatment of ABMR in kidney transplant recipients

Mark D. Stegall

Paradigm



- 50% of patients with DSA develop ABMR
- More common with higher levels/C1q+
- More common with anti-Class II DSA (?Dq)
- Not all patients with DSA lose their grafts: more common with non-adherence
- DSA+/ABMR- patients do well
- cAMR is the major cause of graft loss

Mark D. Stegall

- No effective treatment: we need trials

- We need surrogate endpoints

- The **histologic changes** of cABMR are a good surrogate biomarker for allograft loss because they precede allograft loss by years, are not seen in other conditions that affect the allograft, and are highly predictive of the outcome.
- Alternatively, just use **DSA** alone
- Prevention of graft loss or decline in eGFR is the ultimate goal

Mark D. Stegall

DSA as the inclusion criteria: Weibe et al

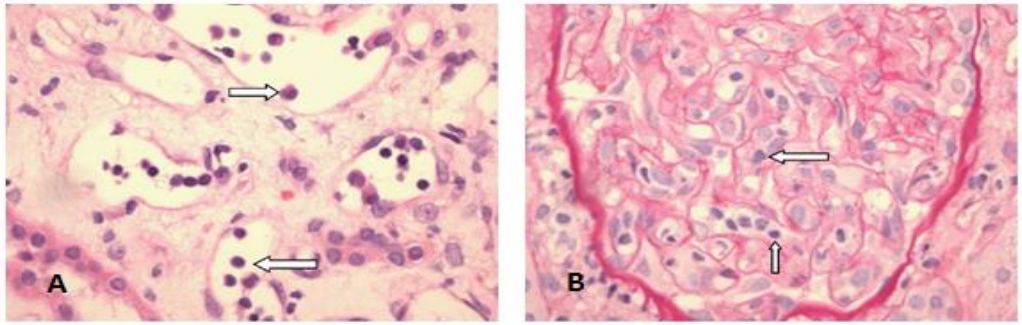
- 40% lost their graft by **5 years** post-dnDSA.
- RCT expected to improve 5 year graft survival by 25% would require 150 recipients (power =80%, drop out 10%, $p<0.05$)
- Declining GFR as an endpoint also suggested

Two big problems:
DSA can resolve without treatment
Rate of graft loss is low

Wiebe C et al. Am J Transplant 2012; 12: 1157.

Intervention Trial Design

- Identify patients with de novo DSA
- Biopsy



  - If ABMR→ Enter into trial
  - If no ABMR→ follow and rebiopsy

Primary Endpoint: Resolution of ABMR

Mark D. Stegall

cABMR Study: Power Calculations

- cABMR does not spontaneously resolve
- 35.7% lose grafts at 2 years

Treatment	Histologic Response	Sample Size		Clinical Endpoint	Sample Size	
		80%	90%		80%	90%
Control	0%	11	14	35.7%	96	128
Drug A	50%	11	14	17.9%	96	128
Total		22	28			

Phase II—signal detection Phase III—graft survival/registry trial

Mark D. Stegall

Which drug to use in the study?

- Wouldn't it be better to study multiple drugs?
- What about **drug combinations**?
- Possible with **adaptive trial design**
- Only use the most effective regimen in the larger Phase III clinical trial

Potential endpoints for response to treatment of ABMR in heart transplant recipients

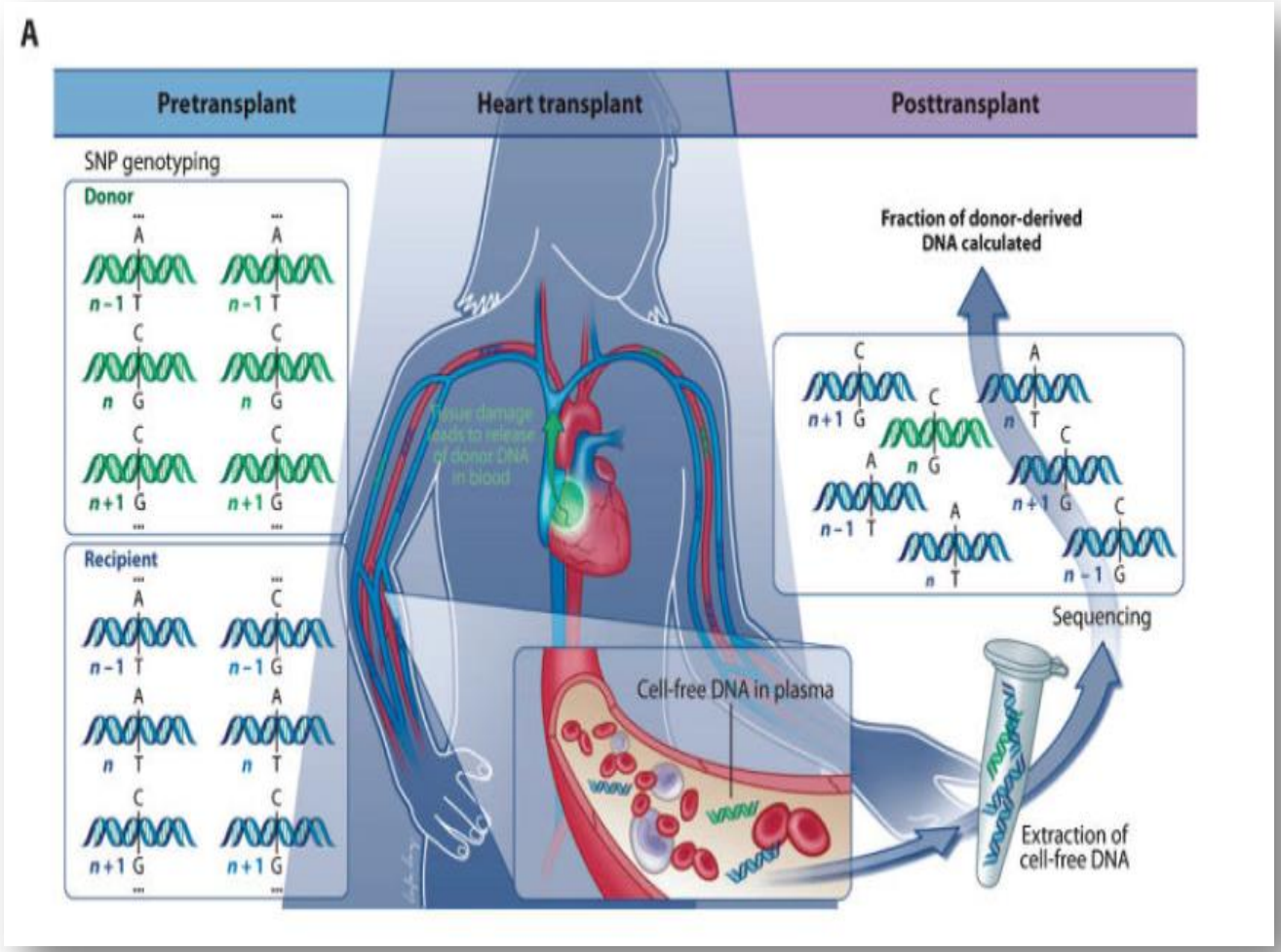
Luciano Potena

Current problems for endpoint definition in cardiac AMR

- Definition of AMR
  - Definition of a target population at high risk of AMR related events
- Identification of the therapeutic target
  - DSA
  - Mechanisms of DSA mediated injury
  - Consequences of DSA mediated injury
- Identification of the clinical target
  - AMR per se (e.g. new onset AMR, relapse AMR)
  - Clinical consequences of AMR
    - Death/graft loss
    - Graft function
    - Graft injury

Luciano Potena

Cell free DNA: a novel intriguing biomarker



De Vlaminck I *Sci Transl Med*. 2014 June 18; 6(241): 241ra77

Role of biomarkers

- Blood biomarkers of graft injury or immune activation (including DSAs) cannot be sufficient for the *diagnosis* of the disease
- Diagnosis require direct and comprehensive analysis of the graft (tissue sampling, coronary angio, EKG, echo)
- Biomarkers are promising to stratify patients at risk
- Clearance of biomarkers (cfDNA in particular) could represent a reliable surrogate for disease resolution after treatment

Luciano Potena

Role of pathologic AMR as endpoint

- pAMR grading is reasonably reproducible and predicts prognosis, but is missing additional info embedded in the tissue morphology
- pAMR describes pathology findings: graft function need to be taken into account for disease definition
- Molecular profiling may reconciliate most of these pitfalls by identifying tissue molecular signature which is related to graft function

Luciano Potena

The ideal endpoint

	pAMR	cfDNA	DSA	Graft function	Molecular profiling
Clinically relevant	+/-	+/-	+/-	+++	+ ? ?
Easy to Measure	+	+/-	+	++/-	-
Objective	+/-	++	+/-	+	+
Enough frequent	+	?	-	+/-	?
Related to diagnosis	+/-	--/+	+	-- /+	++
Related to mechanism of action of the treatment	+/-	- /+	+	--	++

Luciano Potena

Proposals for AMR trial in HT

- Definition of AMR:
  - Injury biomarkers or signs of graft dysfunction + Histology and/or molecular profile

- Endpoints – short term
  1. Function recovery
  2. Biomarker clearance
  3. Molecular profile/histology clearance
- Endpoints – long term
  1. Recurrence of AMR/CHF symptoms
  2. Changes in EKG
  3. Death/graft loss

Luciano Potena

Challenges related to AMR in liver tx

Sandy Feng

Challenges related to AMR in liver tx

- Historical bias
- Diagnostic difficulty
- Lack of (high quality) data
  - Often single center
  - Typically cross-sectional
  - Associative with outcomes
  - Essentially no treatment data

Sandy Feng

Challenges related to AMR in liver tx

- No HLA typing
- No preTx DSA
- Not frequent postTx DSA
- Diagnostic difficulty: is this DSA preformed or de novo?

….. slow progress

Sandy Feng

Recommendations on best practices for pathology endpoints in clinical trials

Robert Colvin

Recommendations on best practices for pathology endpoints in clinical trials

- Participate in the design and choice of endpoints
- Panel of pathologists (3 optimal)
- Adjudication mechanism
- Whole slide digital images
- Auditable assessments (scoring)
- Granular scoring (for clues on mechanism, subsets that respond to therapy)
- Quantitate changes (#, % not categorical 0-3)
- Central lab IHC stains/molecular analysis
- Save unstained sections/blocks for follow-up studies

Robert Colvin

The Molecular Microscope Diagnostic system (MMDx™) as an endpoint for clinical trials

Phil Halloran

What the clinician needs to know about a troubled transplant

Rejection

- T cell-mediated rejection (TCMR)
- Antibody-mediated rejection (ABMR)
- Probability of non-adherence
- Guidance for therapy

Parenchymal injury ("wounding")

- Recent parenchymal injury (AKI)
- Irreversible consequences of previous injury (atrophy-scarring)
- Risk of progression to failure

Phil Halloran

Histology: poor inter-observer agreement provides an estimate of "noise": true error rate

- "Normal vs. abnormal": good
- diagnosis in abnormal: not good e.g. when one pathologist diagnoses T cell mediated rejection, will a second pathologist diagnose cell-mediated rejection:
  - kidney transplant: 50% [1]
  - heart transplant: 28% [2]
  - lung transplant: 0-18% [3]
  - liver transplant?

1. J. Reeve et al. Molecular diagnosis of T cell-mediated rejection in human kidney transplant biopsies. *Am J Transplant 13 (3):645-655, 2013.*
2. M. G. Crespo-Leiro et al. Concordance Among Pathologists in the Second Cardiac Allograft Rejection Gene Expression Observational Study (CARGO II). *Transplantation 94 (11):1172-1177, 2012.*
3. S. M. Arcasoy et al. Pathologic interpretation of transbronchial biopsy for acute rejection of lung allograft is highly variable. *Am.J.Transplant. 11 (2):320-328, 2011.*

Phil Halloran

The Molecular Microscope Diagnostic System (MMDx)™

A central diagnostic system that uses microarrays to measure transcript changes in biopsies (stabilized in RNAlater, shipped Fedex room temp). RNA is extracted, read, and the computer applies equations to compare the biopsy to a Reference Set, generating an automated report in 24 hours.

The report gives probabilistic estimates:

- **Rejection Score (TCMR and/or ABMR)**
- **T cell-mediated rejection (TCMR) Score**
- **Antibody-mediated rejection (ABMR)**
- **Probability of non-adherence**

- **Acute kidney injury (AKI) Score**
- **Extent of irreversible damage (Atrophy-scarring Score)**
- **Risk Score for progression to failure**

Phil Halloran

Advantages and insights from MMDx™

- Much less tissue needed: safety
- Objective, quantitative, probabilistic
- International standard for assessment
- Correct errors in histology
  - C4d, v-lesions, need for DSA
- Estimates functional disturbance: injury
- Mechanisms and druggable targets
- “Theranostic” support: drug development

Phil Halloran

Real time central assessment of kidney transplant indication biopsies by microarrays: The INTERCOMEX Study

Philip F. Halloran[1.2], Jeff Reeve[1], Enver Akalin[3], Olivier Aubert[4], Georg A. Bohmig[5], Daniel Brennan[6], Jonathan Bromberg[7], Gunilla Einecke[8], Farsad Eskandary[5], Clement Gosset[4,9], Jean-Paul Duong Van Huyen[4], Gaurav Gupta[10], Carmen Lefaucheur[4,9], Andrew Malone[6], Roslyn B. Mannon[11], Daniel Seron[12], Joana Sellares[12], Matthew Weir[7], and Alexandre Loupy[4,13]

AJT under review March 2017

INTERCOMEX: Accuracy assessments for MMDx report signed out by PFH prediction of histologic diagnosis of rejection[a]

Agreement with histologic diagnosis of:	sensitivity	specificity	PPV	NPV	Accuracy	**Balanced Accuracy[b]**
ABMR[c]	70%	84%	51%	92%	81%	**77%**
TCMR[c]	62%	93%	45%	96%	90%	**77%**
Rejection	78%	74%	90%	54%	77%	**76%**

[a] using only the 504 (of 519) biopsies where histologic diagnoses were available

[b] the average of the sensitivity and specificity

[c] Mixed rejection was considered a positive call for both ABMR and TCMR in both MMDx and histology. Both totals are > 504 because each diagnosis of "mixed" counts twice. N for MMDx: ABMR(100), TCMR(42), NR(374). Total = 516. N for histology: ABMR(136), TCMR(58), NR(326). Total = 520.

Phil Halloran

Breaking it down into the acute/active ABMR, chronic active ABMR, and chronic (inactive) ABMR, plus ABMR suspicious categories suggest there is a problem with this classification: extensive overlaps

Back to the drawing board

This time use MMDx as an independent test to guide choices

Proposed new data-driven Banff <u>Thursday</u>

Archetypal analysis 1208 kidneys

Phil Halloran

MMDx™ in clinical trials

Vienna- bortezomib in chronic ABMR
Vienna - monoclonal anti C1s in chronic ABMR
Paris – eculizumab in early ABMR
(Several others in planning)

Phil Halloran

Advantages of MMDx™ assessment in clinical trials

- Objective, probabilistic
- Centralized: huge advantage for multi-center trials
  - having central pathologist has never been successful
- High reproducibility/replication
- Adds statistical power, potentially reducing N, $
- What effects could MMDx™ assess in clinical trials?
  - Reduce rejection molecular activity
  - Reduce injury molecular signals
    - Correlate with progression
    - Cannot be assessed by histology

Phil Halloran

Defining an integrative prognostication system and surrogate endpoint in kidney TX

Alexandre Loupy

- Need for more successful therapeutic RCTs in solid organ transplantation
- Need for relevant endpoints
- Need for surrogate endpoints in KT: faster, easier, cheaper
- Need for prognostication systems in organ Tx
- Need for composite surrogate endpoints….

Alexandre Loupy

Integrative Smart data approach: **The iBox**

- Prospective
- Multicenter
- Unselected
- Universal protocol biopsies
- Extensively phenotyped
- Precision diagnoses
- DSA assessment
- Cutting edge technologies
- Kinetics & time line
- Follow-up
- Events

- Performance
- Calibration
- Validation (internal & external)
- Integrative nomograms
- Artifiial neural network
- Decision trees
- Machine learning
- Changes with therapeutics

Alexandre Loupy

Banff process 2017-2017: moving to therapeutics

- Operational validation in real life and clinical trials
- Composite surrogate end point Banff working group
- Banff task force for connecting with regulatory agencies
- Therapeutics in solid organ transplant: successful RCTs

- Integration path towards integrated diagnostics and prognostication system
- From pure pathology to clinics
  - +++HLA system and other biomarkers
  - +++Molecular diagnostics
  - +++Smart data and applied statistics

Alexandre Loupy

….looking forward Banff 2017 conclusions…

Hospital del Mar

Parc de Salut MAR Barcelona

The NEW ENGLAND JOURNAL of MEDICINE

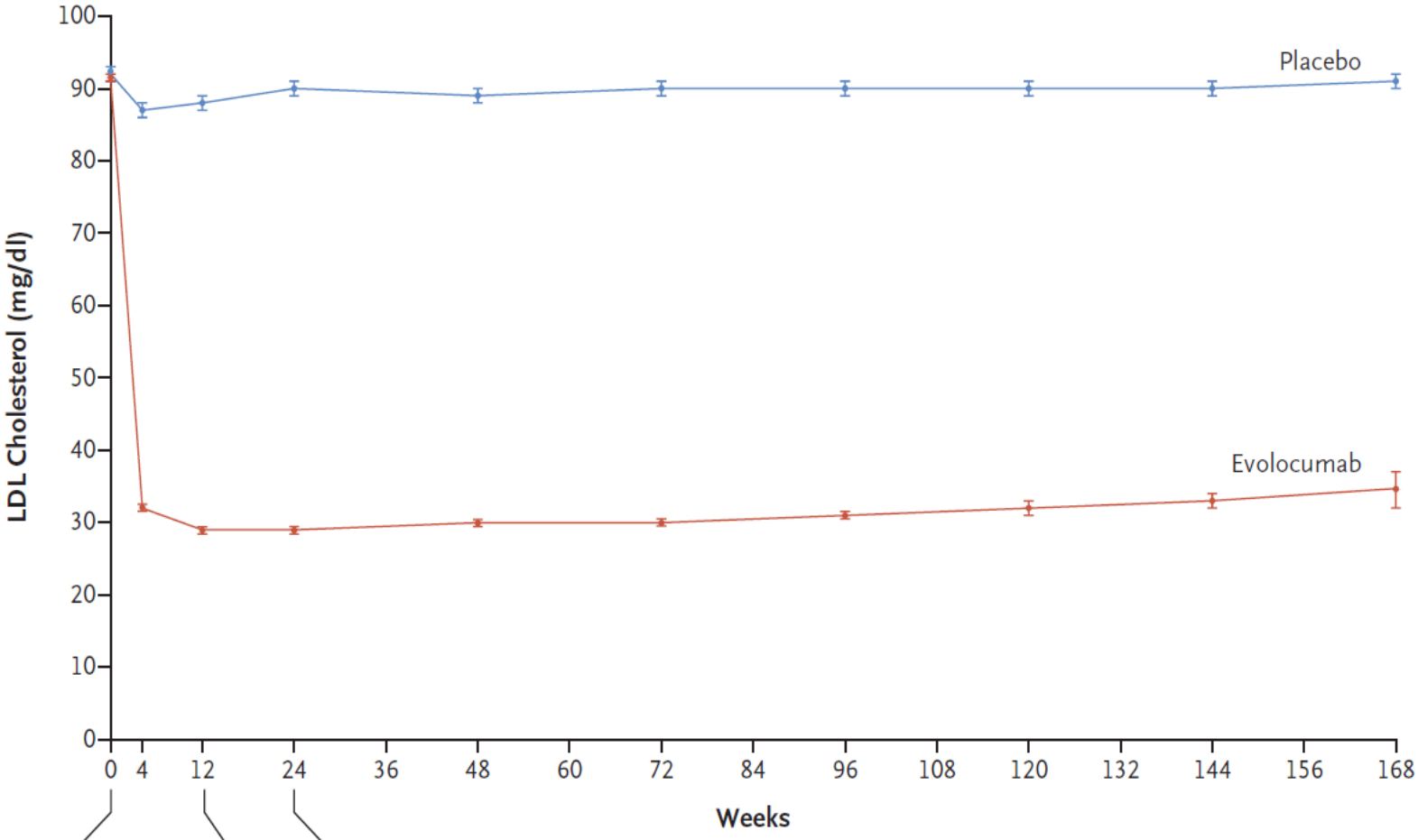
ORIGINAL ARTICLE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

This article was published on March 17, 2017, at NEJM.org.

DOI: 10.1056/NEJMoa1615664

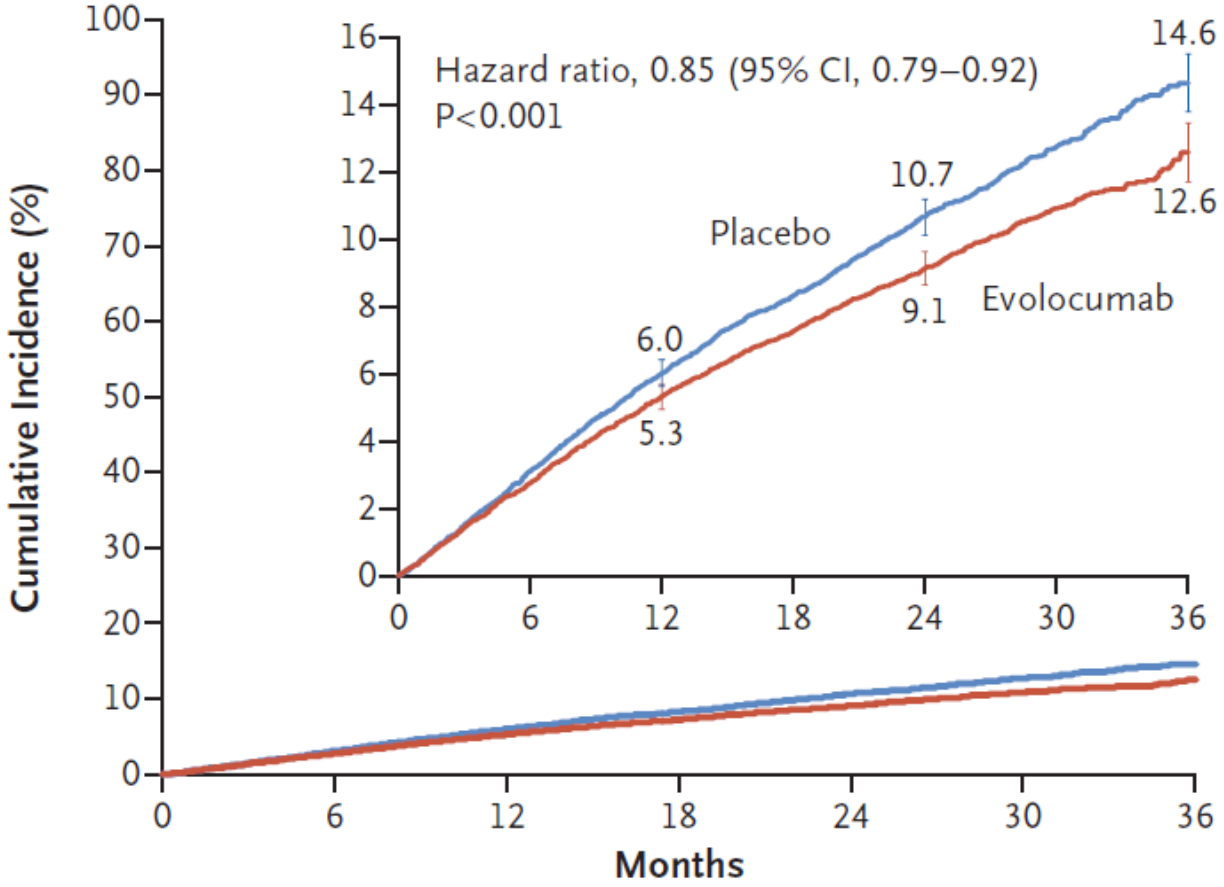


No. at Risk										
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768

This article was published on March 17, 2017, at NEJM.org.

DOI: 10.1056/NEJMoa1615664

A Primary Efficacy End Point



No. at Risk

Placebo	13,780	13,278	12,825	11,871	7610	3690	686
Evolocumab	13,784	13,351	12,939	12,070	7771	3746	689

This article was published on March 17, 2017, at NEJM.org.

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