How to implement Banff Lesions Scores as new endpoints in clinical trials

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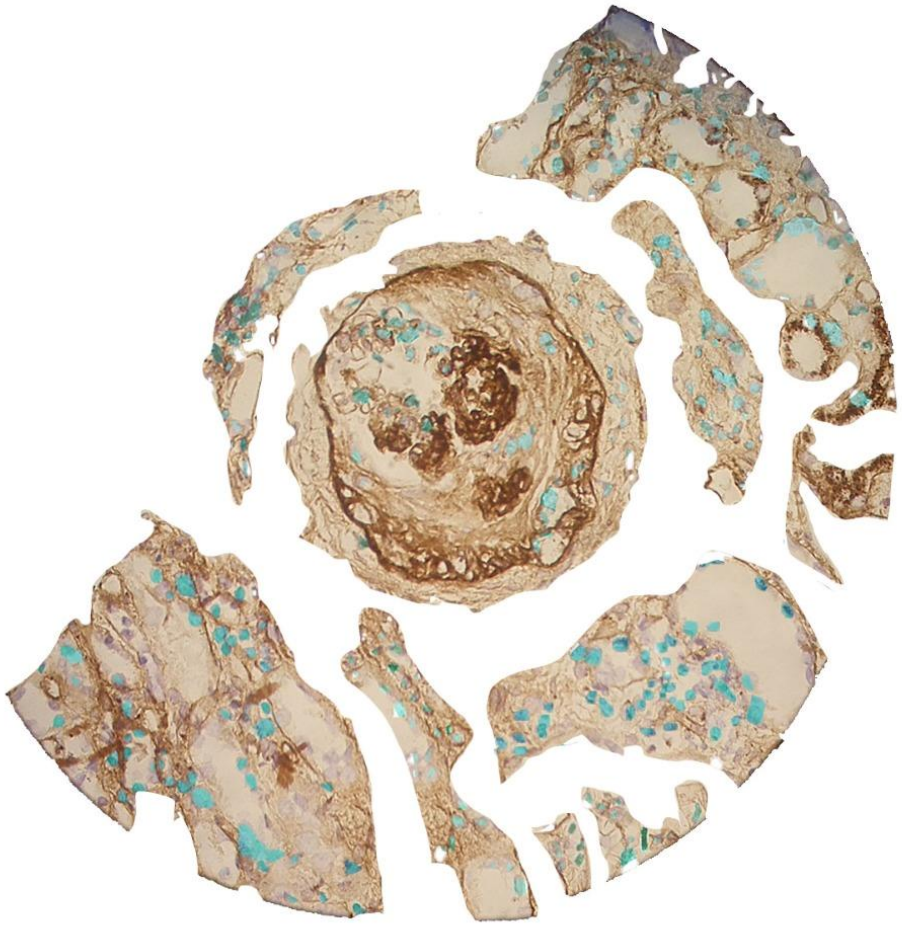

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SOCIETAT CATALANA DE TRASPLANTAMENT

Objectives

The Banff Classification: Diagnostic Categories and Lesion Scores

“Biopsy-proven rejection” (BPAR) as an endpoint : Problems & Solutions

Banff Lesions Scores as Endpoints

Objectives

The Banff Classification: Diagnostic Categories and Lesion Scores

“Biopsy-proven rejection” (BPAR) as an endpoint : Problems & Solutions

Banff Lesions Scores as Endpoints

Kidney International, Vol. 44 (1993), pp. 411–422

International standardization of criteria for the histologic diagnosis of renal allograft rejection: The Banff working classification of kidney transplant pathology

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Standardization of allograft biopsy interpretation is necessary to guide therapy in transplant patients and to help establish an objective rejection end point in clinical trials. Stimulated by

1991 Banff Classification for Allograft Pathology

BANFF INTERNATIONAL CLASSIFICATION OF RENAL ALLOGRAFT PATHOLOGY. K. Solez*, H. Benediktsson, J.F. Burdick, A.H. Cohen, R.B. Colvin, B.P. Croker, P.F. Halloran*, P. Hayry, P.A. Keown, B.D. Myers, C.C. Nast, S. Olsen, L.C. Racusen, E.L. Ramos, S. Rosen, and E. von Willebrand, for the Int. Society of Nephrology Commission on Acute Renal Failure. (*U. of Alberta, Edmonton, Canada)

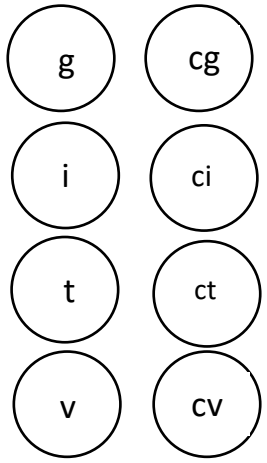
Working from a core document developed by Drs. Croker, Olsen, Racusen, and Solez, a group of renal pathologists, nephrologists, and surgeons met in Banff, Canada Aug. 2-4, 1991 to develop a schema for international standardization of nomenclature and criteria for the histologic diagnosis of renal allograft rejection. Further input was obtained after the meeting and the schema was validated by the circulation of a set of 50 slides for coding by participant pathologists. In this schema intimal arteritis and tubulitis are accepted as the principal lesions indicative of acute rejection. Glomerular, interstitial, tubular, and vascular lesions of acute rejection and "chronic rejection" are graded 0-3+, to produce a gitv (acute) or cg ci ct cv (chronic) coding for each biopsy. Principal diagnostic categories are 1) normal, 2) hyperacute rejection, 3) borderline changes, 4) acute rejection (mild, moderate, severe), 5) chronic transplant nephropathy (chronic rejection) (mild, moderate, severe), and 6) other. It is hoped that this standardized classification will facilitate the performance of multicenter trials in renal transplantation.

This abstract has not been published or submitted for presentation at another meeting.

SIGNATURE:

SAMPLE FORMAT:

Solez et al. KI 1993

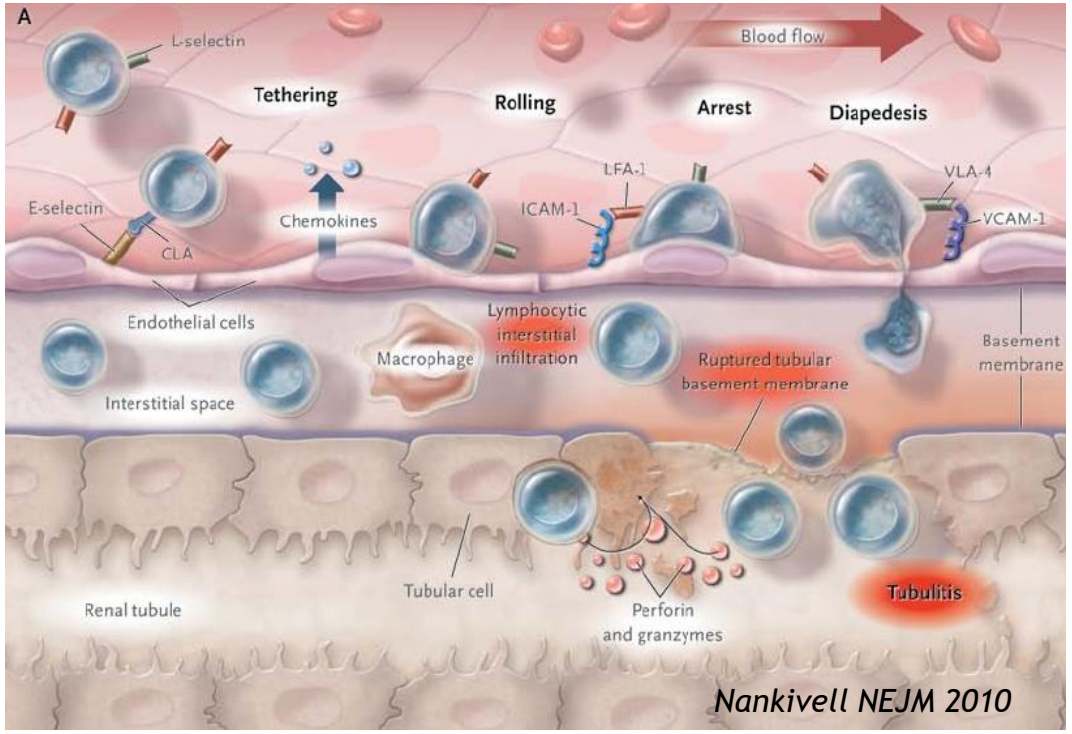


Banff lesion scores
Semi-quantitative grading of biopsy features
Not specific per se

Banff diagnostic categories
Grouping of features indicative of underlying pathophysiological process

- Normal
- Hyperacute rejection
- Borderline changes
- Acute rejection
- Chronic transplant nephropathy “chronic rejection”
- Other

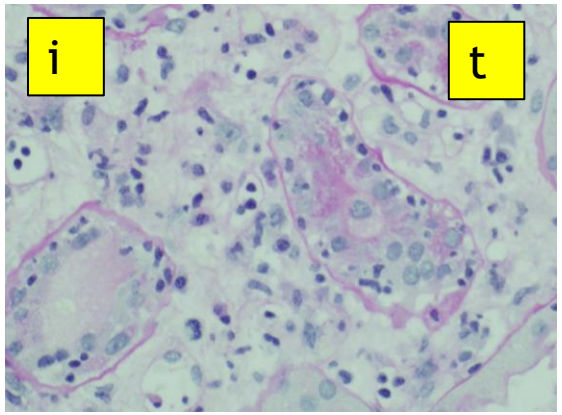
BL/TCMR

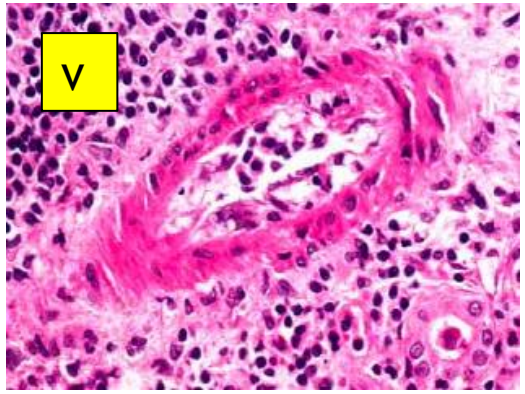


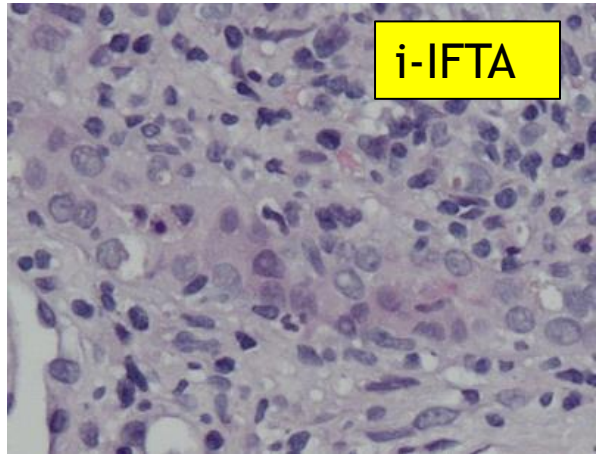
Diagnostic category

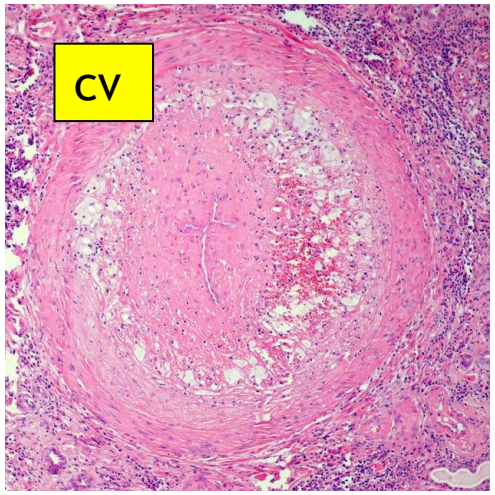
"Acute TCMR"

"Chronic active TCMR"

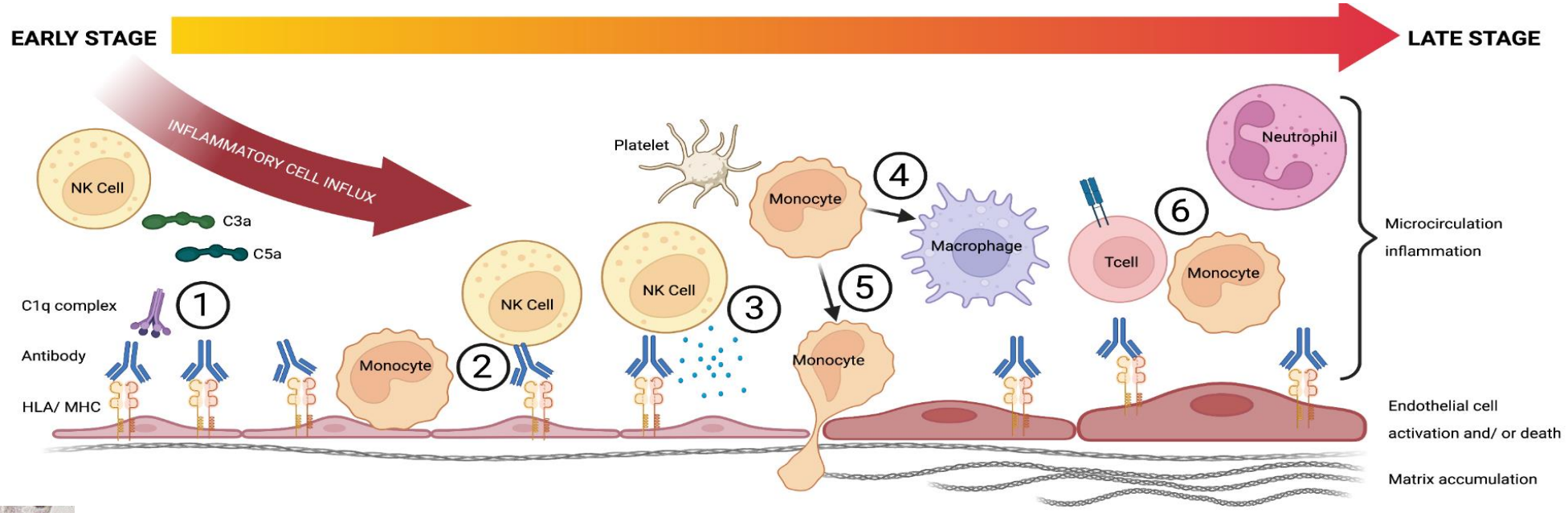




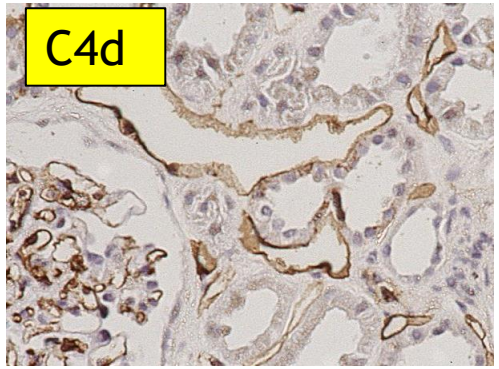


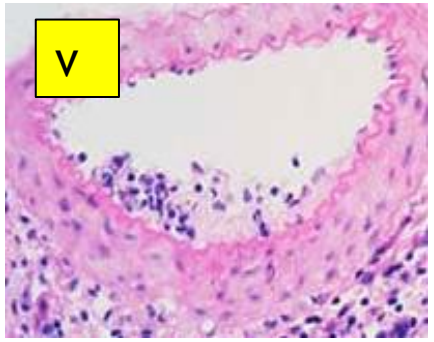


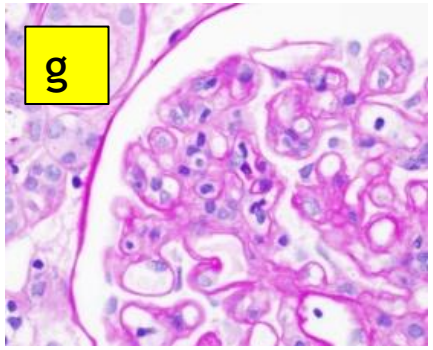
AMR

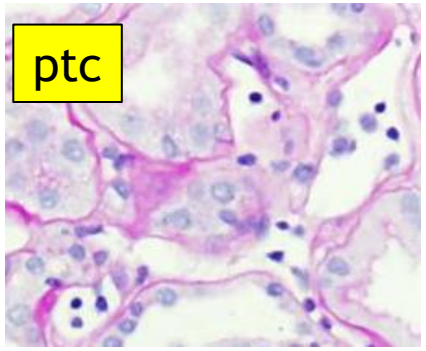


"Acute AMR"

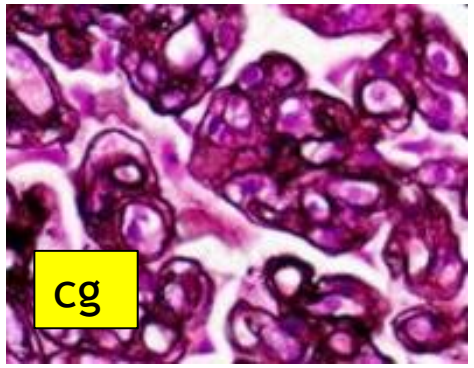


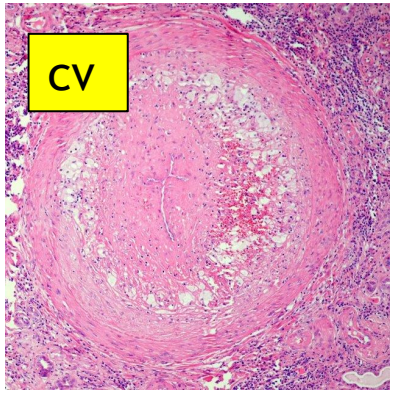


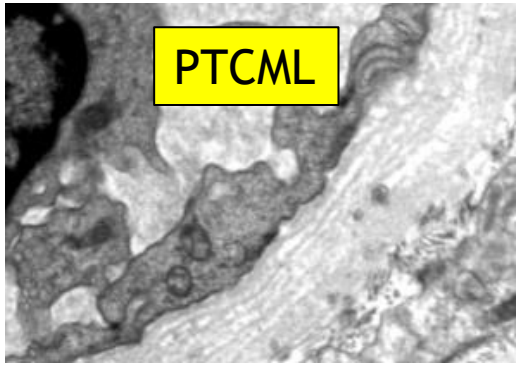




"Chronic (active) AMR"







BANFF lesion scores - activity

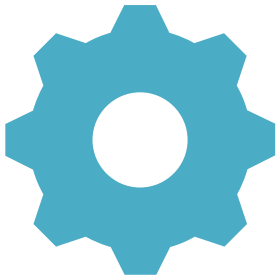
- t – tubulitis
- i,ti, i-IFTA – interstitial inflammation
- v – arterial inflammation
- g – glomerulitis
- ptc - peritubular capillaritis

BANFF lesion scores - chronicity

- ct – tubular atrophy
- ci – interstitial fibrosis
- cv- intimal fibrosis
- cg – glomerular double contours
- ptcml – ptc basement membrane changes

BANFF lesions scores - other

- ah – arteriolar hyalinosis
- C4d – Immunohistochemical staining score



BANFF CATEGORIES

- **1. Normal**
- **2. Antibody-mediated rejection**
- **3. Borderline**
- **4. T-cell mediated rejection**
- **5. Interstitial fibrosis/tubular atrophy**
- **6. Other (e.g. BK NP, recurrent GN etc.)**

How reproducible is it?

Inter-observer kappa scores

Banff Lesions

- ptc score
  - 0.32-0.43 (*Gibson I et al. AJT 2008; 8: 819–825*)
  - 0.38 (*Smith et al Transplant International 2019; 32: 173–183*)
- g score
  - 0.31 (*Haas et al. Banff 2013 meeting report AJT 2014*)
  - 0.39 (*Smith et al. Transplant International 2019; 32: 173–183*)
- cg score
  - 0.47 (*Haas et al. Banff 2013 meeting report AJT 2014*)
  - 0.48 (*Smith et al. Transplant International 2019; 32: 173–183*)

Diagnostic Categories

- Active AMR = 0.70 (*Smith et al. Transplant International 2019; 32: 173–183*)
- Chronic, active AMR = 0.59 (*Smith et al. Transplant International 2019; 32: 173–183*)

Objectives

The Banff Classification: Diagnostic Categories and Lesion Scores

“Biopsy-proven rejection” (BPAR) as an endpoint : Problems & Solutions

Banff Lesions Scores as Endpoints

Clinical trial Endpoints

- Endpoint = variable intended to reflect an outcome of interest
- *Must be precisely defined to yield reliable and reproducible results*
- How have Banff Diagnostic Categories and Banff Lesion scores been used as ?
  - Primary endpoint
  - Secondary endpoint
  - Surrogate endpoint

- Primary endpoint
  - Used for study statistical design - power calculation (sample size)
  - Can be composite

  FDA and EMA both accept "BPAR" as a primary or composite primary endpoint

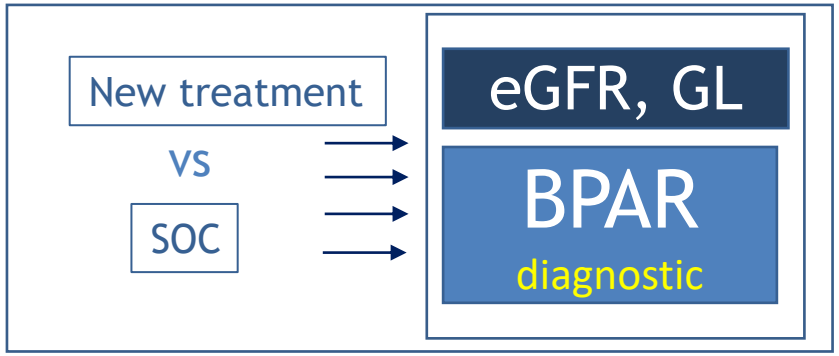
- Secondary endpoint
  - Other outcomes of interest
  - Do not have the same statistical authority; higher likelihood of chance observations

  BPAR or Lesion scores on follow-up biopsies

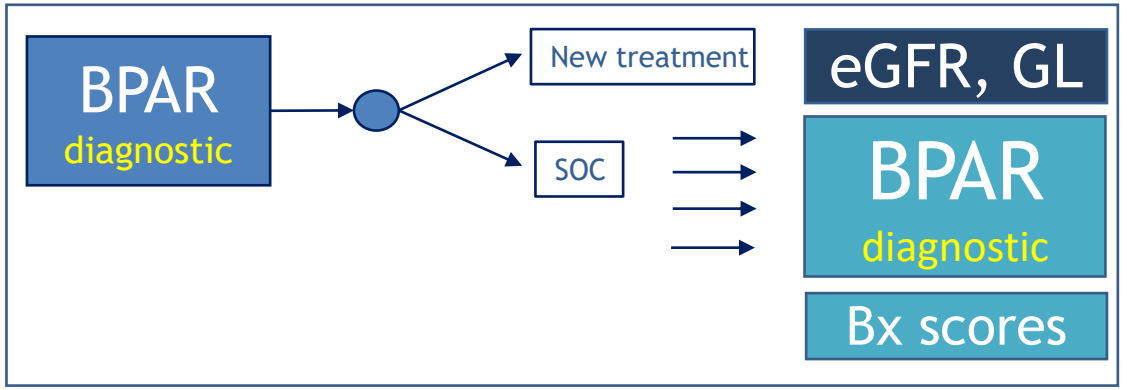
- Surrogate endpoint
  - Biomarker that predicts and "explains" the subsequent primary end point
  - Prognostic features

  Lesion scores may be useful in combination with other features

Prevention of rejection



Treatment of rejection



Secondary

…must be precisely defined to yield reliable and reproducible results…

precisely defined ?

- "BPAR" (FDA/EMA) contains BL/TCMR and AMR
- Each Banff category contains a lot of things
  - Active and chronic active?
  - Are we including the incomplete/borderline categories?
  - Subclinical as well as clinical?
- For some Banff categories, definitions have changed over time

- > Trials do not always follow Banff definitions

Interventional studies for prevention of early AMR (pre-formed/sensitised)

Ref	Protocol	Recruitment	AMR endpoint	Results
Marks et al AJT 2019	RCT Eculizumab vs SOC C10-001	Sensitised living donor	Primary: composite of AMR grade II/III, graft loss, death, or loss to follow-up < 9 weeks post-Tx	NS difference between eculizumab and SOC for AMR grades II/III Significant when grade I AMR included
Glotz et al AJT 2019	single arm Eculizumab C-10-002	Deceased donor, preformed DSA	Primary: composite AMR grade II/III, graft loss, death, or loss to follow-up, < 9 weeks post-Tx	Significantly lower treatment failure rate than expected for standard
Vo et al. Transplantation 2015	phase I/II open label pilot IVIg + tocilizumab	Unresponsive to desensitisation with rituximab + IVIg	Secondary: Rejection (AMR or TCMR) in post-Tx Bx, NOS (Primary = transplanted)	Only 1 case of AMR, NOS
Cornell et al AJT 2015	Eculizumab+PEx vs historical control PEx	Positive XM living donor	Secondary = Banff lesions scores, clinical and subclinical AMR over subsequent years (Primary = histopathologic features of acute tissue injury attributable to alloantibody in first 3 months)	NS difference at later timepoints for C4d, subclinical AMR and Banff lesions score between groups
Stegall et al AJT 2011	Eculizumab+PEx vs historical control PEx	Positive XM living donor	Primary = incidence clinical Banff 2003 AMR first 3 month (Secondary = later AMR, cg)	Significantly lower acute AMR in Eculizumab vs controls Significantly lower cg at 1 year

precisely defined - the example for AMR

- "AMR" endpoint definition variable
- Effect of treatment not being consistently measured
- This makes it difficult to compare clinical trials

- Are Banff AMR definitions fit-for-purpose of use as endpoints in clinical trials?

ESOT | Transplant International

Redefining Risk Stratification and Endpoints for Clinical Trials in Kidney Transplantation: Rationale and Methodology of Proposals Submitted to the European Medicines Agency by the European Society for Organ Transplantation

Maarten Naesens[1], Stefan Schneeberger[2] and the ESOT Working Group*

Evolution of the Definition of Rejection in Kidney Transplantation and Its Use as an Endpoint in Clinical Trials

*Jan Ulrich Becker[1†], Daniel Seron[2†], Marion Rabant[3], Candice Roufosse[4] and Maarten Naesens[5]**

Proposed Definitions of Antibody-Mediated Rejection for Use as a Clinical Trial Endpoint in Kidney Transplantation

*Candice Roufosse[1†], Jan Ulrich Becker[2†], Marion Rabant[3], Daniel Seron[4], Maria Irene Bellini[5], Georg A. Böhmig[6], Klemens Budde[7], Fritz Diekmann[8], Denis Glotz[9], Luuk Hilbrands[10], Alexandre Loupy[11], Rainer Oberbauer[6], Liset Pengel[12], Stefan Schneeberger[13] and Maarten Naesens[14]**

Proposed Definitions of T Cell-Mediated Rejection and Tubulointerstitial Inflammation as Clinical Trial Endpoints in Kidney Transplantation

*Daniel Seron[1†], Marion Rabant[2†], Jan Ulrich Becker[3], Candice Roufosse[4], Maria Irene Bellini[5], Georg A. Böhmig[6], Klemens Budde[7], Fritz Diekmann[8], Denis Glotz[9], Luuk Hilbrands[10], Alexandre Loupy[11], Rainer Oberbauer[12], Liset Pengel[13], Stefan Schneeberger[14] and Maarten Naesens[15]**

Summary: broad agreement with Committee for Medicinal Products for Human Use (CHMP)

- “BPAR” no longer accurate as an endpoint
  - rejection type is a useful specification – borderline, TCMR and AMR
- Improve Diagnostic definitions in order to provide reliability and reproducibility needed for clinical trials

-> Banff Working Group for Clinical Trial Endpoints

Banff recommendations on best practices for pathology endpoints in clinical trials

- Pathologists to participate in the design and choice of endpoints
- Panel of (central) pathologists (3 optimal to avoid a tie)
- Sufficient clinical information to (central) pathologists for correct diagnosis, including detailed information on DSA status for AMR diagnosis
- Adjudication mechanism (how discordance between pathologists is addressed)
- Whole slide digital images for centralized slide review
- Auditable assessments (scoring that can be reviewed and audited externally)
- Granular scoring and reporting of all Banff lesions, not only final Banff diagnostic category (detailed phenotyping and lesions scoring considered for ***secondary*** endpoints)
- Quantitate changes (use of continuous scores and percentages rather than semi-quantitative scoring)
- Centralized processing of ancillary testing, e.g., IHC stains

Loupy et al. AJT 2017

Objectives

The Banff Classification: Diagnostic Categories and Lesion Scores

“Biopsy-proven rejection” (BPAR) as an endpoint : Problems & Solutions

Banff Lesions Scores as Endpoints

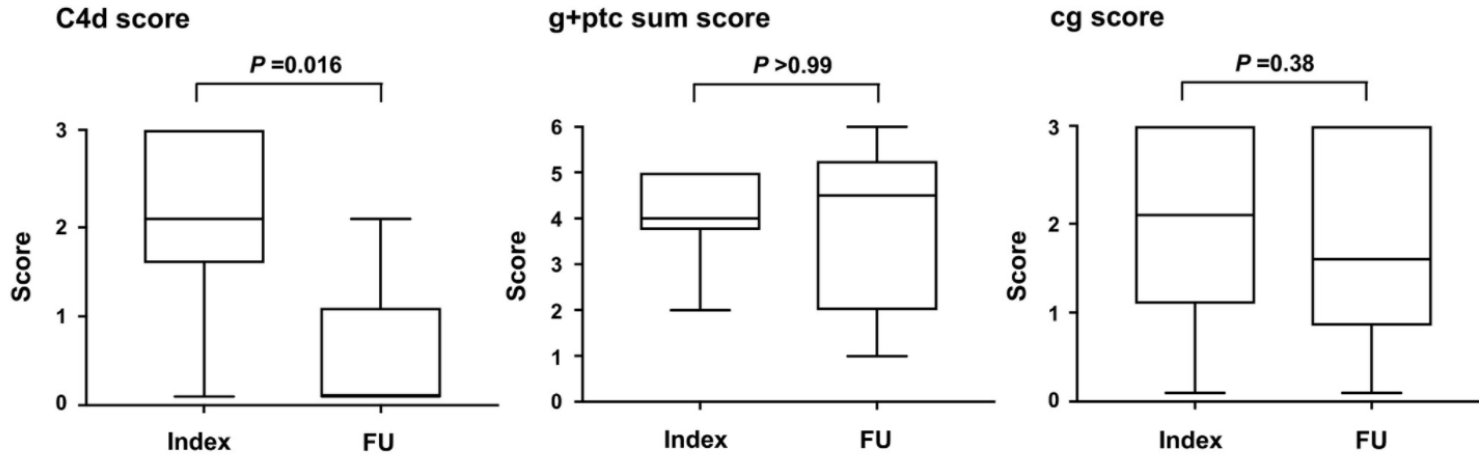
Banff lesion scores as endpoints

- Enrolment /Primary endpoint
  - No
- Secondary endpoints
  - Yes - Does treatment reduce active lesions and/or block development of chronic lesions?
- Surrogate endpoint
  - Yes
    - Do active or chronic lesions after treatment predict long term outcome?
    - On their own or in combination with other features? -> i-Box

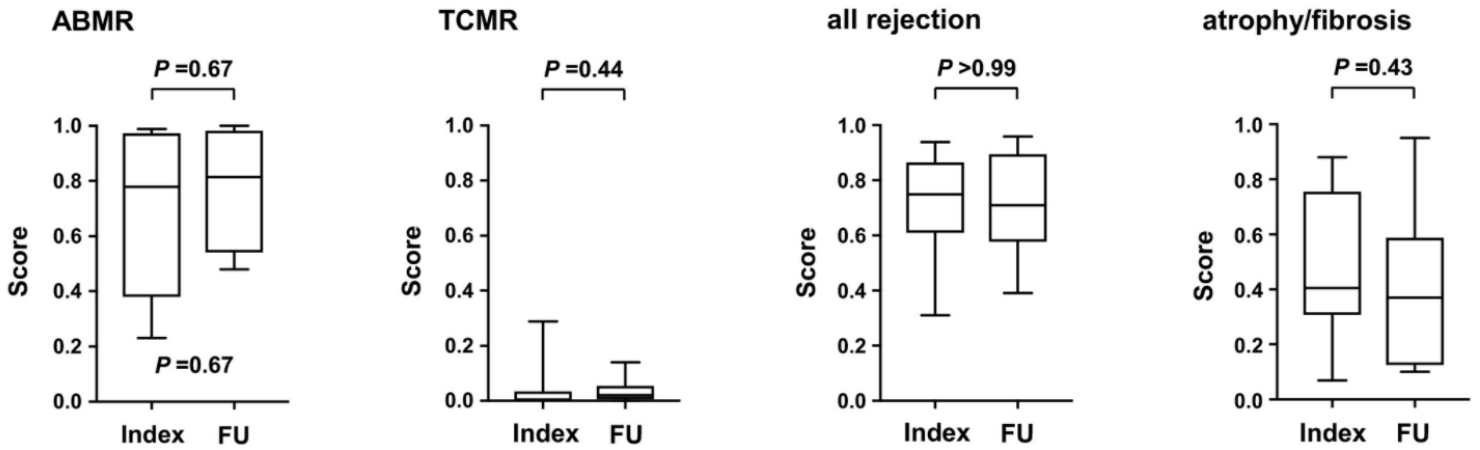
Reference	Drug	Result
Eskandary JASN 2017	Bortezomib	NS changes comparing groups for diagnosis and individual scores
Eskandary AJT 2018	anti-C1s	Significantly less C4d post Rx NS for MVI, gene expression
Sautenet Transplantation 2016	Rituximab (RITUX-ERAH)	NS difference comparing treatment groups for IFTA and g+ptc; Significant increase IFTA post Rx in placebo group only
Viglietti AJT 2016	C1-INH + IvIg in refractory AMR	NS compared to historical control group Significantly less C4d post Rx NS for MVI, cg, IFTA
Choi AJT 2017	Tocilizumab	Significant improvement g+ptc pre/post treatment
Moreso AJT 2018	Rituximab TRITON	NS comparing treatment groups NS pre and post Rx
Montgomery AJT 2016	C1-INH	Both groups improvement pre/post treatment; NS decrease TG at 6 months
Kumar Transplantation 2021	Belatacept conversion	NS pre and post-Rx "All rejection" gene score improved NS trend towards improved AMR score
Doberer et al. JASN 2020	clazakizumab	Early Bx: NS differences for Banff scores and Late Bx: Significant decrease in MMDx AMR and rejection scores in clazakizumab group; NS for MVI score
Lavacca et al. Clin Tx 2020	Tocilizumab	Significant reduction in g NS change in cg, C4d, or IFTA pre and post Rx

anti-C1s

Conventional scores

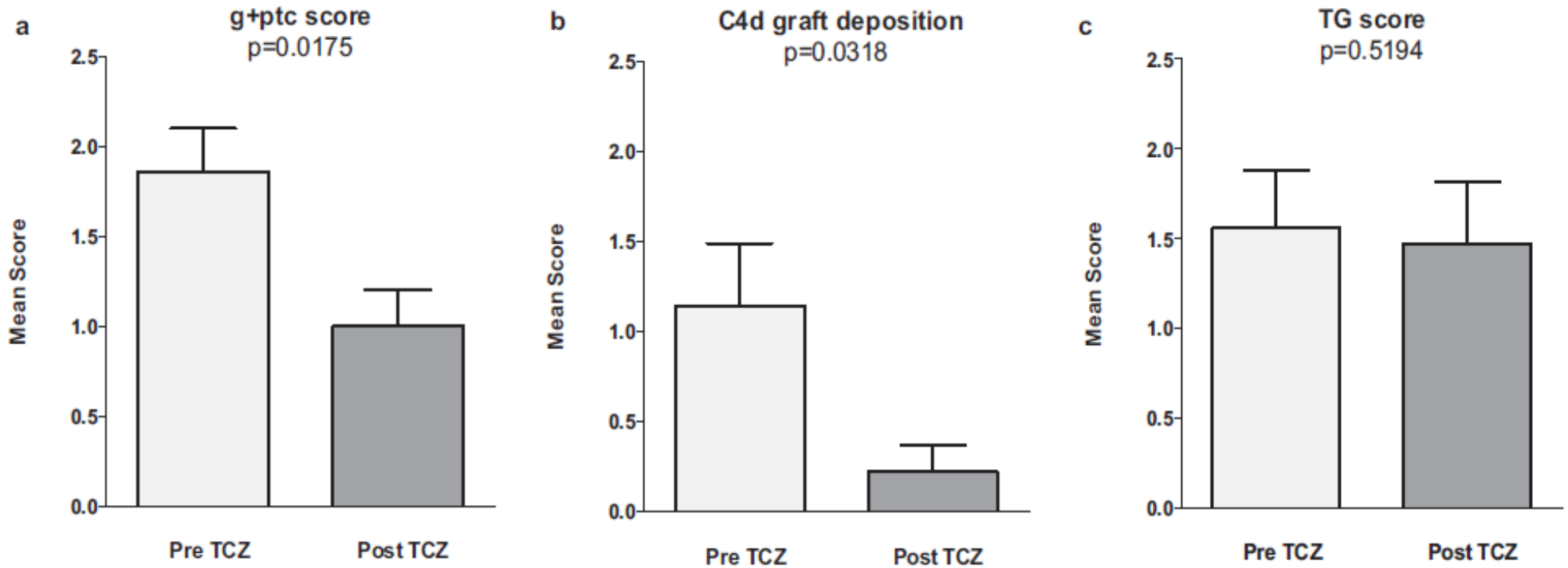


Molecular scores



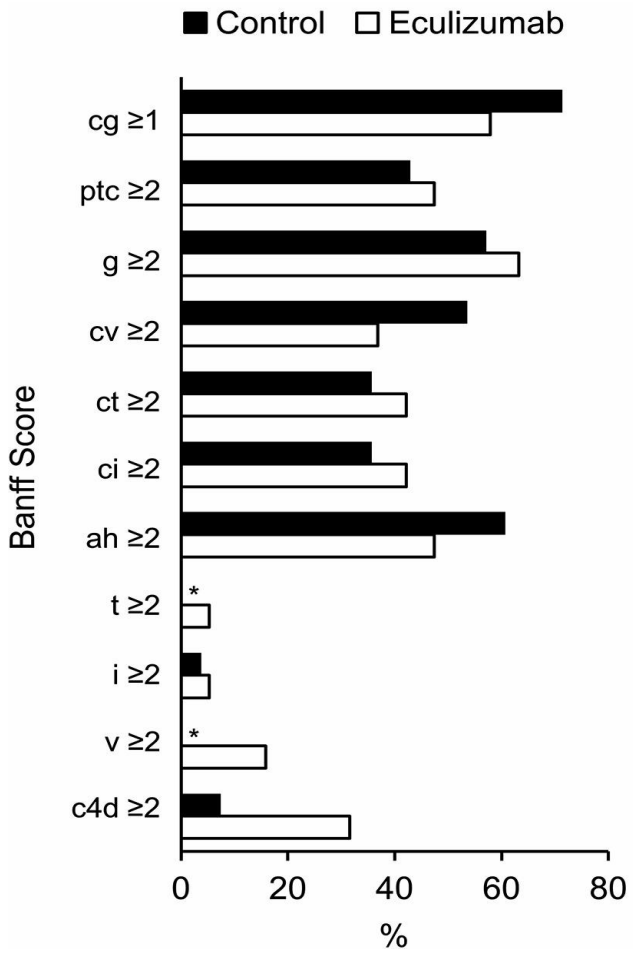
Eskandary et al. AJT 2018

Tocilizumab - Significantly less inflammation



Choi et al AJT 2017

Long-term outcomes of eculizumab-treated positive crossmatch recipients



	Eculizumab +XM (%) (n=19)	Control +XM (%) (n=28)	*P Value*
Chronic ABMR cg score ≥0	57.9 (11)	71.4 (20)	.36
Peritubular capillaritis ptc score ≥2	47.4 (9)	42.9 (12)	.77
Glomerulitis g score ≥2	63.2 (12)	57.1 (16)	.77
Vascular intimal thickening cv score ≥2	36.8 (7)	53.6 (15)	.37
Tubular atrophy ct score ≥2	42.1 (8)	35.7 (10)	.76
Interstitial fibrosis ci score ≥2	42.1 (8)	35.7 (10)	.76
Arteriolar hyalinosis ah score ≥2	47.4 (9)	60.7 (17)	.39
Tubulitis t score ≥2	5.3 (1)	0.0 (0)	.40
Inflammation i score ≥2	5.3 (1)	3.7 (1)	1.0
Intimal arteritis v score ≥2	15.8 (3)	0.0 (0)	.06
C4d ≥2	31.6 (6)	7.4 (2)	.05

Reduction in early active ABMR in eculizumab-treated recipients with a positive BFXM

No reduction in chronic CAMR or improve death-censored allograft survival

Stegall AJT 2011; Schinstock AJT 2019

Banff Lesions Scores as part of other indices

i-Box (Alex Loupy and PTG)

Vaulet et al. (Leuven) JASN 2021- semi-supervised clustering of Banff lesion scores reveals novel phenotypes

Activity and chronicity indices for AMR (Haas KI 2023)

- Activity = g + ptc + v + C4d
- Chronicity = ci + ct + ci + 2xcg

Summary

How to implement Banff Lesions Scores as new endpoints in clinical trials

- Banff Classification Diagnostic Categories are used as primary or secondary endpoints
  - Diagnostic definitions should be reliable and reproducible
  - As much as possible, should group together cases with the same underlying pathophysiological process
- Banff Lesions Scores may be useful as secondary endpoints and surrogate endpoints
  - None are specific for a diagnosis
  - Some predictive of outcome
  - Some may change with treatment
  - Report granular scores +/- indices
- Follow the Banff Recommendations for pathology endpoints in Clinical Trials

Thank you!