MAYO CLINIC

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

DSA vs Histology

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Disclosures

- Ad Board—Novartis, Roche, Astellas
- Mayo Contract—Transplant Genomics, Inc.

Overall Goal

- To Improve the Outcomes of Transplant Recipients
- Clinical Endpoints: How they feel, function and survive

Disclaimer

- I am not primarily interested in diagnostics
- I am primarily interested in therapy
- Thus, I am interested in being able to do feasible studies to evaluate the efficacy of therapy to prevent graft loss due to chronic antibody mediated rejection

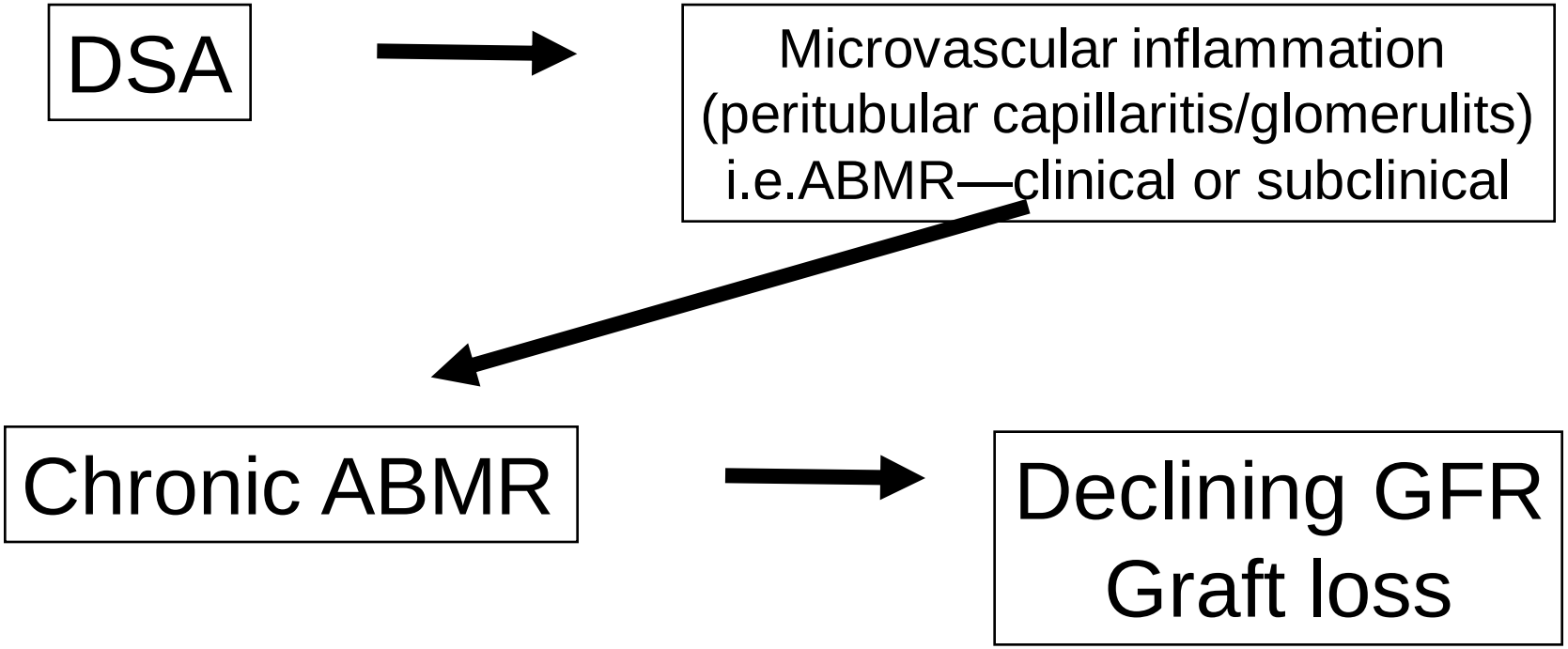
Main Interests—Mathematics

- Enrollment
- Sample size needed to demonstrate efficacy
- Screening population
- Incidence of the problem
- Length of the study: <5 years is imperative
- Not interested in perfection!

Improving Graft Survival

- Difficult to improve 1 year graft survival
- Long-term studies are difficult and expensive
- Common problem in almost all fields of medicine
- Surrogate endpoints/predictive biomarkers

Paradigm


DSA
Microvascular inflammation
(peritubular capillaritis/glomerulits)
i.e.ABMR—clinical or subclinical
Chronic ABMR
Declining GFR
Graft loss

Definitions

- Donor-specific alloantibody
  - LABscreen assay for total IgG
  - Only FDA approved assay
  - Not C1q, subclasses, non-HLA, etc.
- Late, active ABMR (Banff 2013)
  - Not the crescendo acute ABMR early after transplant
- ABMR vs cABMR—microvascular inflammation with/without transplant glomerulopathy
  - Very similar lesions

Banff 2013 criteria

- 1) Histologic evidence of acute tissue injury resulting from ABMR and includes glomerulitis (Banff g score >0) and/or peritubular capillaritis (Banff ptc score >0), intimal or transmural arteritis (Banff v score>0), thrombotic microangiopathy, or acute tubular injury, in the absence of any other apparent cause
- 2) Evidence of current/recent antibody interaction with vascular endothelium including at least one of the following (Banff C4d score ≥2 with immunofluorescence on frozen section or Banff g+ptc score ≥2), and
- 3) Serologic evidence of donor-specific antibodies.
- Haas M, Sis B, Racusen LC, et al. Am J Transplant 2014; 14 (2): 272.

The FDA approves new drugs

- Evidence based
- Prospective, randomized trials
- Clear inclusion criteria
- Clear endpoints

Assumptions: Histology as a Biomarker

- 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 and a consensus among experts
- Might be the pathway to validating other biomarkers (genomics, proteomics, etc).

de Novo DSA

- The incidence varies with the patient population studied and how strictly it is defined.
- 5 years after kidney transplantation, cumulative incidence ranged from 13% (14) to 22% (15).
- Weibe C and Nickerson P. Curr Opin Organ Transp;ant 2013; 18:470-477.

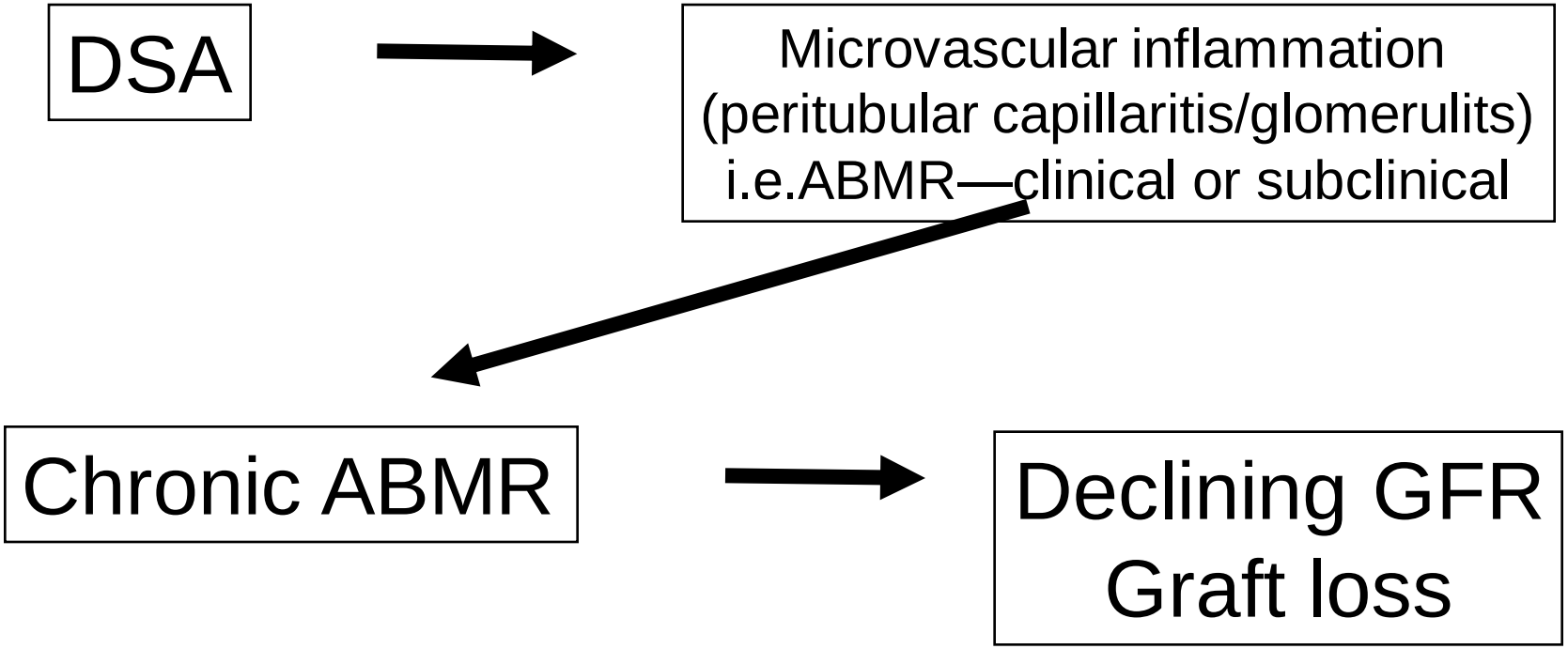
Mechanism of DSA Development

- T cell dependent immune response
- Non-adherence (commonly combined with T cell mediated rejection)→ may persist after treatment/resolution of the cellular response
- Planned reduction in immunosuppression—Polyoma virus, cancer or minimization/tolerance protocols
- Subclinically in otherwise adherent patients (?50% in our series)

What you are left with

- Patient with DSA after the other problems are taken care of
- Now we can go to work

Paradigm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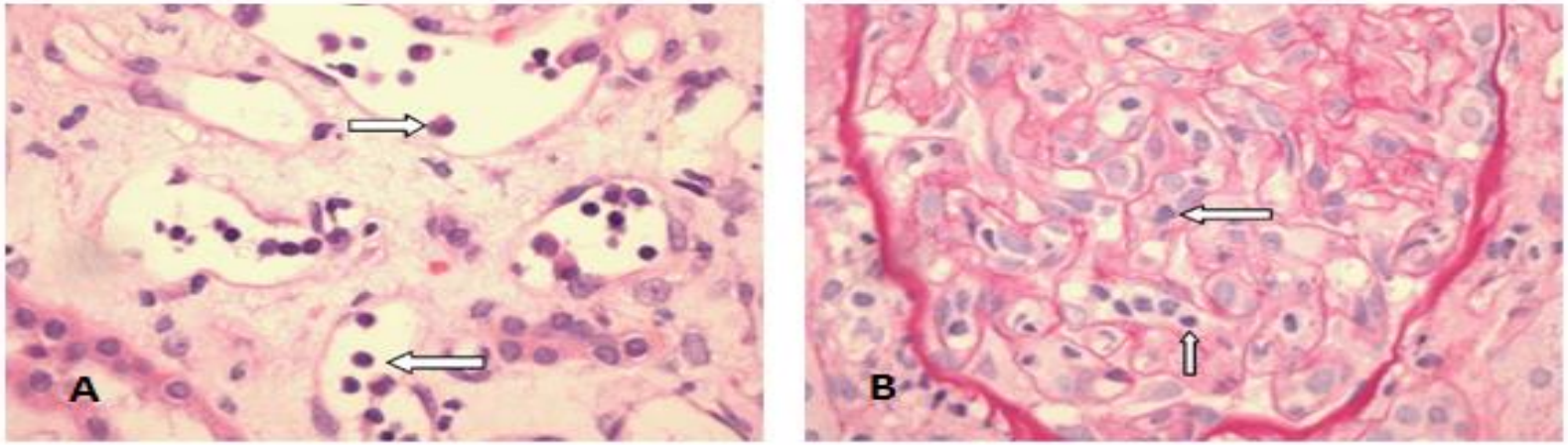
Not All Patients with DSA have Graft Loss

DSA → Microvascular inflammation (peritubular capillaritis/glomerulits) i.e.ABMR—clinical or subclinical

- 50% of patients with DSA develop ABMR
- More common with higher levels/C1q+
- More common with anti-Class II DSA (?Dq)
- DSA+/ABMR- patients do well



Histologic features of Antibody Mediated Rejection. Peritubular capillaritis (leftl A) and glomerulitis (right B) are hallmark histologic features of antibody mediated rejection.

Chronic Antibody Mediated Rejection is the major cause of late graft loss

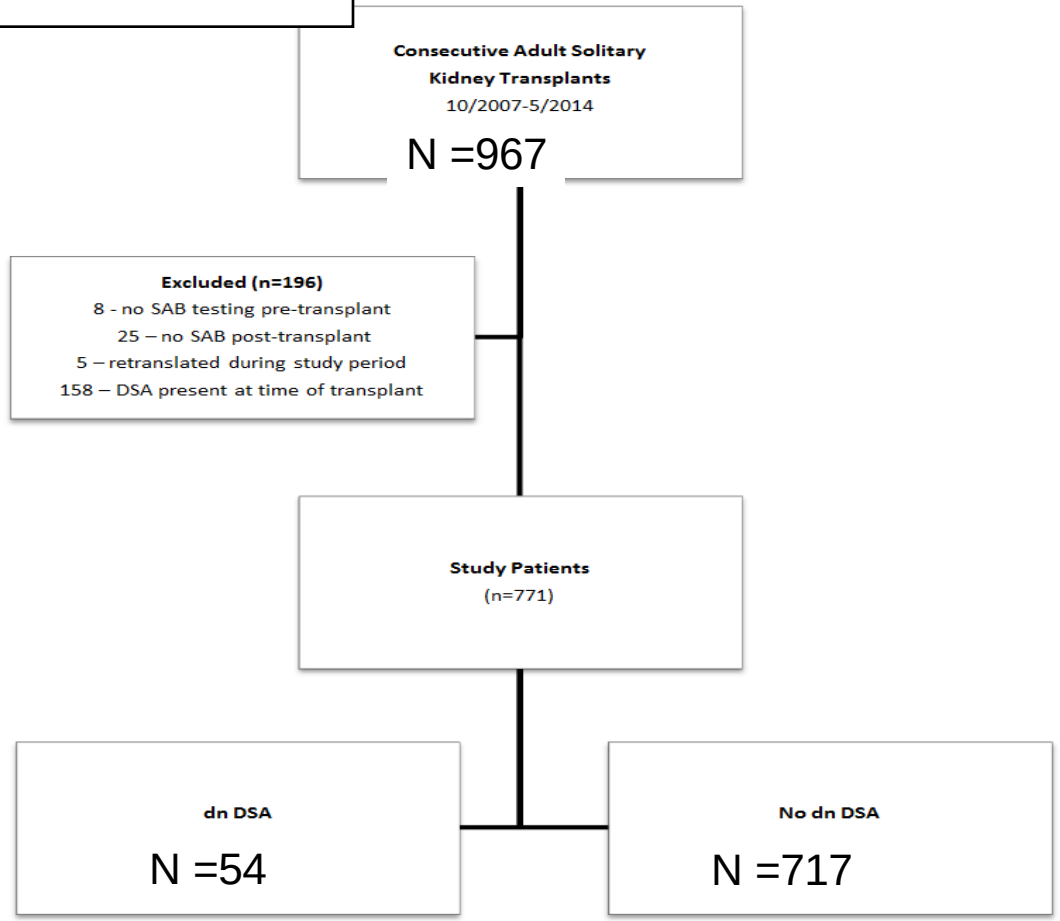
- Transplant glomerulopathy (the signature lesion of cABMR) the most prominent histologic lesion preceding graft loss in 36% of kidney transplant recipients at Mayo Clinic, Rochester, 52% in Belgium and 64% in Edmonton.
- Up to 80% of allografts fail within 5 years of developing cABMR.

- El-Zoghby ZM, Stegall MD, Lager DJ, et al. Am J Transplant 2009; 9: 52.
- Sellares J, De Freitas DG, Mengel M, et al. Am J Transplant 2011; 11: 489.
- Naesens M, Kuypers DR, De Vusser K, et al. Transplantation. 2014; 98: 427.

The Value of Protocol Biopsies to Identify Patients with De Novo Donor Specific Antibody at High Risk for Allograft Loss.

- Schinstock CA, Cosio F, Cheungpasitporn W, et al.
- *Am J Transplant. 2016 Dec 15*. doi: 10.1111/ajt.14161. [Epub ahead of print]

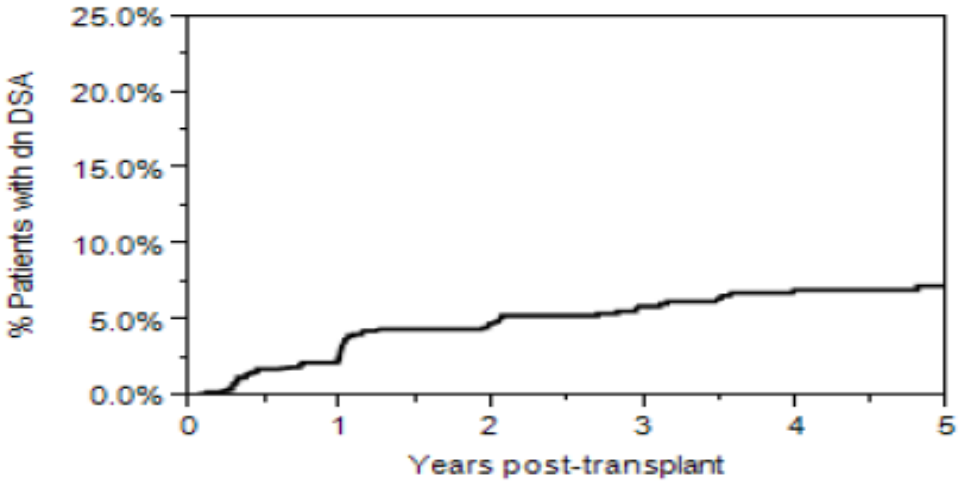
De Novo DSA



Yearly DSA testing
Surveillance biopsies
1, 2, 5 years and when DSA detected

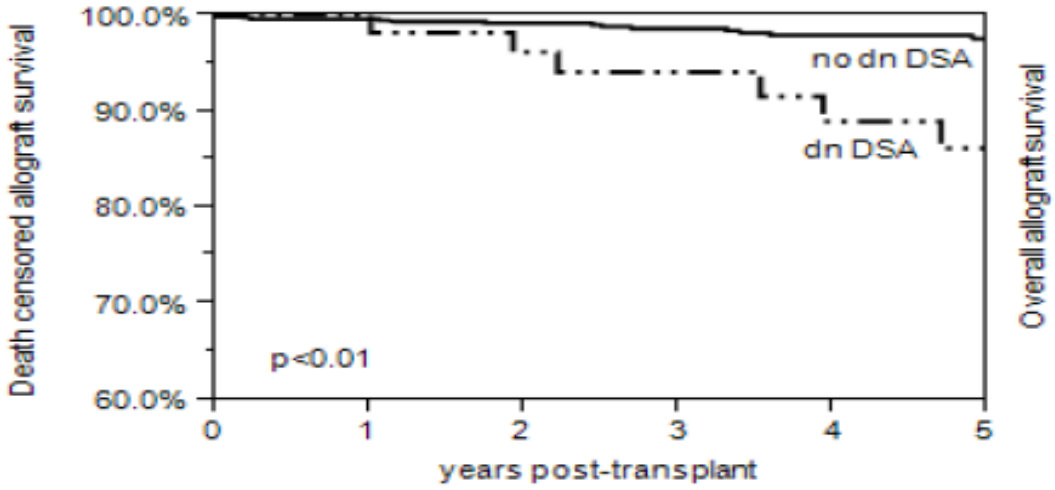
Mean Follow-Up
4.2±1.9 years

Time to de novo DSA detection



Is dnDSA lower in Tacrolimus-treated patients than in cyclosporine-treated patients? Unknown

Death-Censored Allograft Survival



Surveillance Biopsies
1 year after dnDSA detection

- 53% had acute, active ABMR (normal Creatinine)
- 37% had cABMR (cg>0)

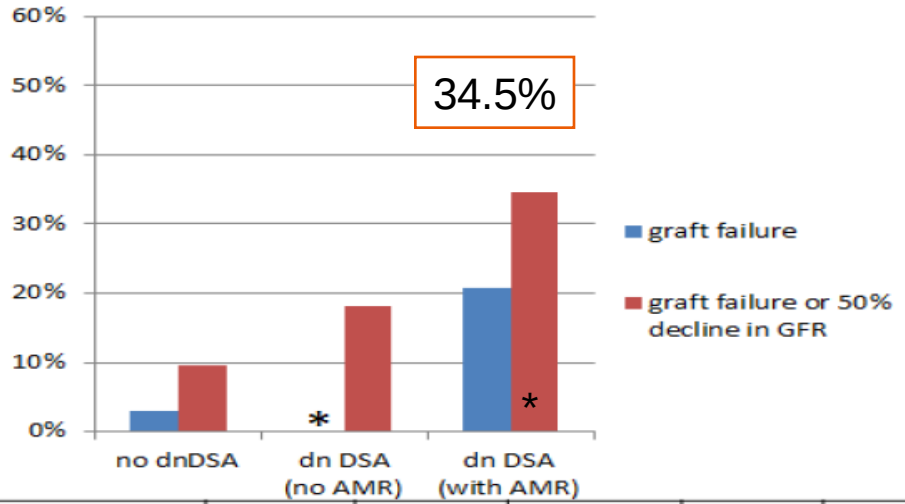
De No ection

Important for study design:

Prevention—treat all, graft loss rates are lower

Intervention—Enriched population, graft loss rates are higher

Easier to show an effect



	no dnDSA	dnDSA No AMR	P-value (compared with no DSA)	dnDSA AMR	P-value (compared with no DSA)
Graft failure	2.9 (21/717)	0 (0/22)	P=1.0	20.7 (6/29)	P<0.01
Graft failure or 50% decline in GFR	9.6 (69/717)	18.2 (4/22)	P=0.26	34.5 (10/29)	P<0.01

Mean f/u after DN DSA Detection 3.5+2.0 years

No Proven Effective Treatment

Treatment of ABMR

CLINICAL AND TRANSLATIONAL RESEARCH

(*Transplantation* 2014;97: 1240–1246)

Late Antibody-Mediated Rejection in Renal Allografts: Outcome After Conventional and Novel Therapies

Gaurav Gupta,[1] Bassam G. Abu Jawdeh,[2] Lorraine C. Racusen,[3] Bhavna Bhasin,[4] Lois J. Arend,[3] Brandon Trollinger,[5] Edward Kraus,[4] Hamid Rabb,[4] Andrea A. Zachary,[4] Robert A. Montgomery,[6] and Nada Alachkar[4,7]

CLINICAL AND TRANSLATIONAL RESEARCH

(*Transplantation* 2014;97: 1253–1259)

High Dose Intravenous Immunoglobulin Therapy for Donor-Specific Antibodies in Kidney Transplant Recipients With Acute and Chronic Graft Dysfunction

James E. Cooper,[1,4] Jane Gralla,[2] Patrick Klem,[3] Laurence Chan,[1] and Alexander C. Wiseman[1]

Transplantation 2008; 86:1754.

Bortezomib Provides Effective Therapy for Antibody- and Cell-Mediated Acute Rejection

Matthew J. Everly,[1] Jason J. Everly,[1] Brian Susskind,[2] Paul Brailey,[2] Lois J. Arend,[3] Rita R. Alloway,[4] Prabir Roy-Chaudhury,[4] Amit Govil,[4] Gautham Mogilishetty,[4] Adele H. Rike,[1] Michael Cardi,[5] George Wadih,[5] Amit Tevar,[1] and E. Steve Woodle[1,6]

We need trials

- What would a trial look like?
- Who to include?
- Who to exclude?
- Endpoints/Surrogate endpoints?
- Adaptive Trial Design

- **A conservative estimate that we used in power calculations for our proposed study is a rate of DSA detection in the overall transplant population of 2%/year after transplantation.**
- This correlates to a 10% incidence at 5 years.

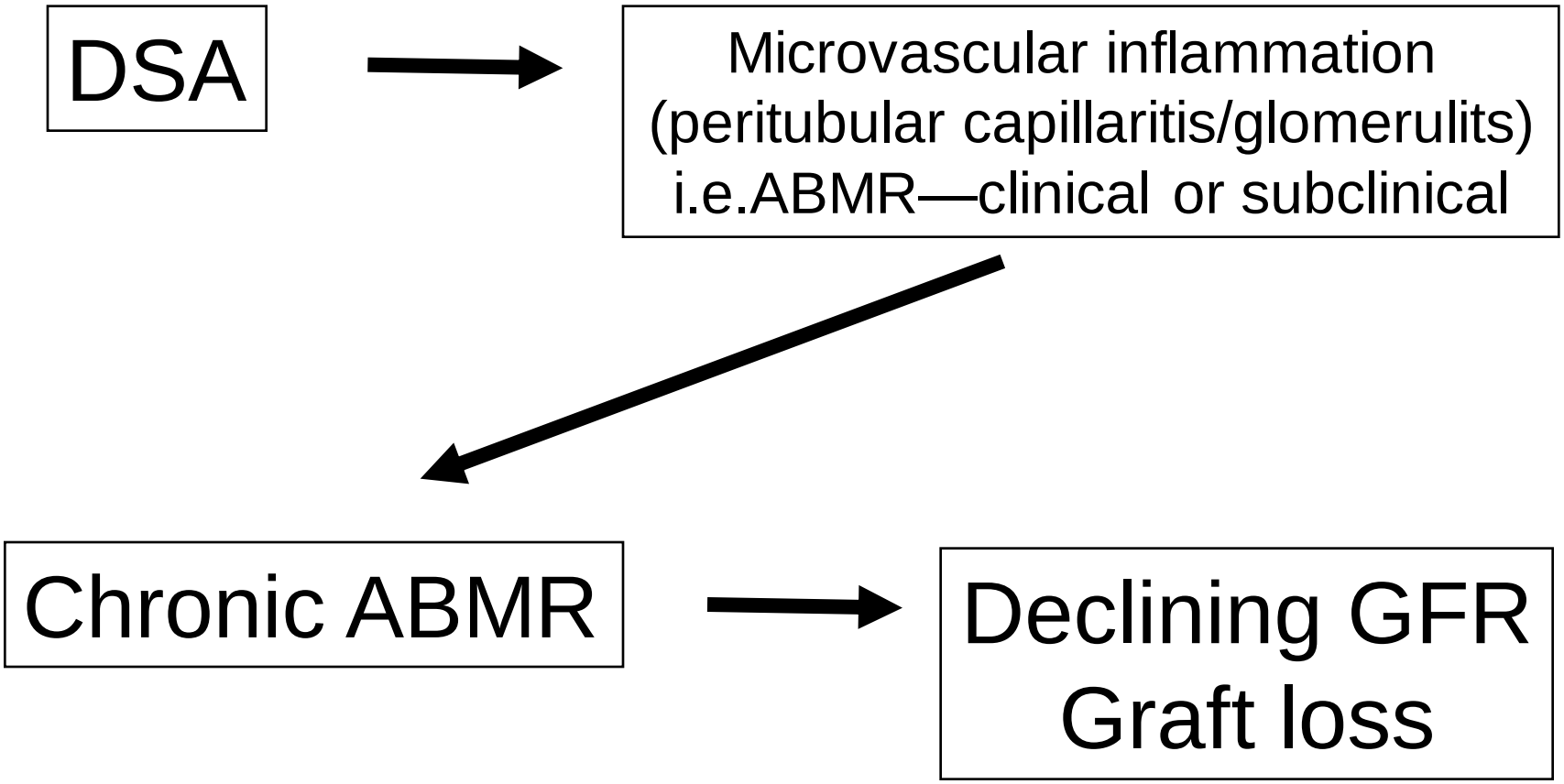
Combined Clinical Endpoints

- Graft loss
- 50% decline in eGFR

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

Paradigm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What about a surrogate endpoint study? Shorten time to show efficacy

Surrogate=resolution of DSA

or

Surrogate=resolution of cAMR on biopsy

Design #1
DSA as the inclusion criteria Intervention Trial

- MFI >1000
- 6 months treatment and recheck DSA
- Treat→ MFI <1000
- Incidence of graft loss with MFI 1000 at **2 years** is 18%

C1q might be better, but not FDA approved

Wiebe et al. Am J Transplant 2016;

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

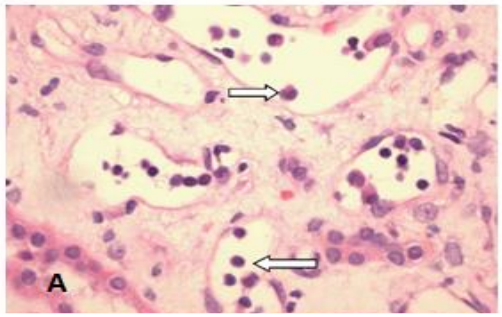
Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. Am J Transplant 2012; 12: 1157.

	DSA Decrease	80%	90%	Clinical Endpoint	80	90%
CTL	20%	43	58	18%	230	308
Rx	50%	43	58	9%	230	308
Total		84	116		460	608

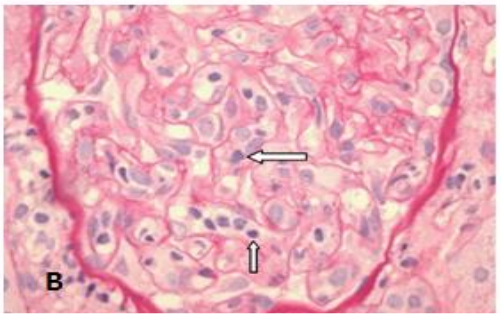
Two big problems:
DSA can resolve without treatment
Rate of graft loss is low

#2 Intervention Trial Design

- Identify patients with de novo DSA
- Biopsy
- If ABMR→ Enter into trial
- If no ABMR→ follow and rebiopsy



Peritubular capillaritis



Glomerulitis

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Primary Endpoint: Resolution of ABMR

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

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

Adaptive Trial Design

- A methodology in which a clinical trial evolves or adapts as the trial proceeds depending on the outcomes of patients enrolled.
- The criteria for these decisions are set prior to the beginning of the studies.
- An adaptive design may use of standard statistical methods (i.e. frequentist) to halt the trial early for toxicity (dangerous substance), futility (no improvement over a control), or efficacy (great improvement over a control).

Adaptive Trial Design

- Can “learn” from relatively small numbers of study subjects.
- In our calculations of cABMR, as few as 8 patients can be used to decide if a therapy is ineffective.
- Another aspect of ATD that enhances efficiency is that it uses a single ongoing control group rather than having a different control group for each experimental group.
- The vast majority of patients can be assigned to an experimental group. This maximizes the number of different studies that can be performed in a small population of patients

Adaptive Trial Design

- Minimizes the number of patients receiving ineffective treatments and thus limits unnecessary treatment risks in study patients. FDA like it
- Cheaper—drug companies like it

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Adaptive Trial Design

	Single Therapy [No Dual therapy]				Dual Therapy [ALL Single therapy fail]			
Therapy	ALL FAIL	1 Works	2 Works	3 Works	ALL FAIL	1 Works	2 Works	3 Works
Control	8	17	17	17	17	17	17	17
Treatment								
1	8	17	17	17	8	8	8	8
2	8	8	17	17	8	8	8	8
3	8	8	8	17	8	8	8	8
Treatment								
1+2					8	17	17	17
1+3					8	8	17	17
2+3					8	8	8	17
	32	50	59	68	65	74	83	92

Remember we need 7/14 to respond

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Feasibility

- 4 years enrollment with 1 year follow up

Solitary Kidney Transplants	*2%/ year with de novo DSA*	*52% of these with ABMR*	*Enrollment Planned*
15,000 follow-up years	*390 new DSA patients*	*202*	*68-100*
DSA Screening population	*Biopsy population*	*Study Screening population*	*Allows for up to a 50% screen failure rate*

Conclusions

- Developing therapy for cABMR is a major unmet need in kidney transplantation
- Validated surrogate markers are needed (histology is a very good one)
- Clinical trials are feasible
- Best to employ adaptive trial design

Reality

- Improving long-term renal allograft survival is a tough problem
- It will take many years to make improvements
- We need to start now
- I may not see the final product