Achieving Desensitization and Preventing Humoral Rejection in Positive Crossmatch Living Donor Kidney Transplantation

Mark D. Stegall
M. Breanndon Moore
James Gloor

Mayo Clinic College of Medicine
Rochester, MN

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Previous reports of positive crossmatch kidney transplants

PP/IVIG

- Montgomery et al. *Transplantation* 2000; 70(6):887-895.
- Schweitzer et al. *Transplantation* 2000; 70 (10): 1531.
- Gloor et al. *Am J Transplant* 2003; 3(8):1017-1023.

High Dose IVIG

- Jordan et al. *Transplantation* 1998; 66 (6): 800.
- Glotz et al. *Am J Transplant* 2002; 2(8):758-760.
- Akalin et al. *Transplantation.* 2005: 79(6):742, 2005

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Aim

Compare the efficacy of

Single high dose of IVIG

Vs.

Plasmapheresis/low dose IVIG

in achieving desensitization and the prevention of humoral rejection in sensitized renal allograft recipients

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Methods

- Retrospective review of sensitized candidates 10/99-4/05 (N=112)
- Excluded
  - T cell AHG-/Flow + (N=35)
  - T cell AHG-/B cell + (N=8)
- Positive T cell AHG Xmatch against living donor
- N=69 entered in 3 different protocols

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Endpoints

- Desensitization

  Negative T cell AHG Xmatch

- Prevention of Humoral Rejection

  Biopsy proven antibody-mediated damage

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High Dose IVIG Desensitization

Current Study	Previous studies
Negative T cell AHG xmatch	Goal=negative NIH
All patients	In vitro "blocking assay"
High-dose IVIG (2g/kg)	same
1 dose in 11/13	May be repeated
	80% transplanted

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Desensitization Protocols

Protocol 1. High Dose IVIG

2 g/kg x 1 on day -1
n=13 8/03-7/04

Protocol 2. Plasmapheresis (PP)

PP daily + low dose IVIG (100mg/kg)
Anti-CD20 day -4
19 splenectomy/13 no splenectomy
n=32 9/99-7/03

Protocol 3. PP/Monitoring

PP, anti-CD20, pretransplant Thymoglobulin, no splenectomy
Monitoring post-tx antibody levels→PP
n=14 8/04-4/05

All: Thymoglobulin (1.5 mg/kg/d x 5) and tacrolimus, mycophenolate mofetil and prednisone

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Desensitization vs. Baseline AHG Titer

Titer	IVIG	PP	PP+ Mon
Undilute			X
1:2	X	XXXXXXXXXXX	XXXXX
1:4	XX	XXXXXXXXXX	XX
1:8	X ++	XX	XXXX
1:16	X ++	XXXX ++++	X
1:32	X ++	+++	
1:64	+		
1:128	+		
1:256			++

X = responder/negative T cell AHG Xmatch

+ = non-responder

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All Patients Respond at Least Partially to IVIG*

	Pre IVIG AHG titer	Post IVIG
Responders	2	0
	4	0
	4	0
	8	0
	16	0
Non-responders	8	8
	8	2
	16	2
	16	8
	32	2
	32	16
	128	32
	256	8

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Results
Desensitization

High dose IVIG

5/13 (36%)*

PP/IVIG +/- Splenectomy

27/32 responded (84%)

PP + Monitoring

14/16 (88%)

P<0.05 vs. PP

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DESENSITIZATION vs. Baseline AHG Titer

Titer	IVIG	PP-based
Undilute		1/1
1:2	1/1	16/16
1:4	2/2	12/12
1:8	1/3 (33%)	7/8 (88%)
1:16	1/3 (33%)	6/11 (66%)
1:32	1/3	0/5
1:64	0/1	
1:128	0/1	0/1
1:256		1/3 with graft loss

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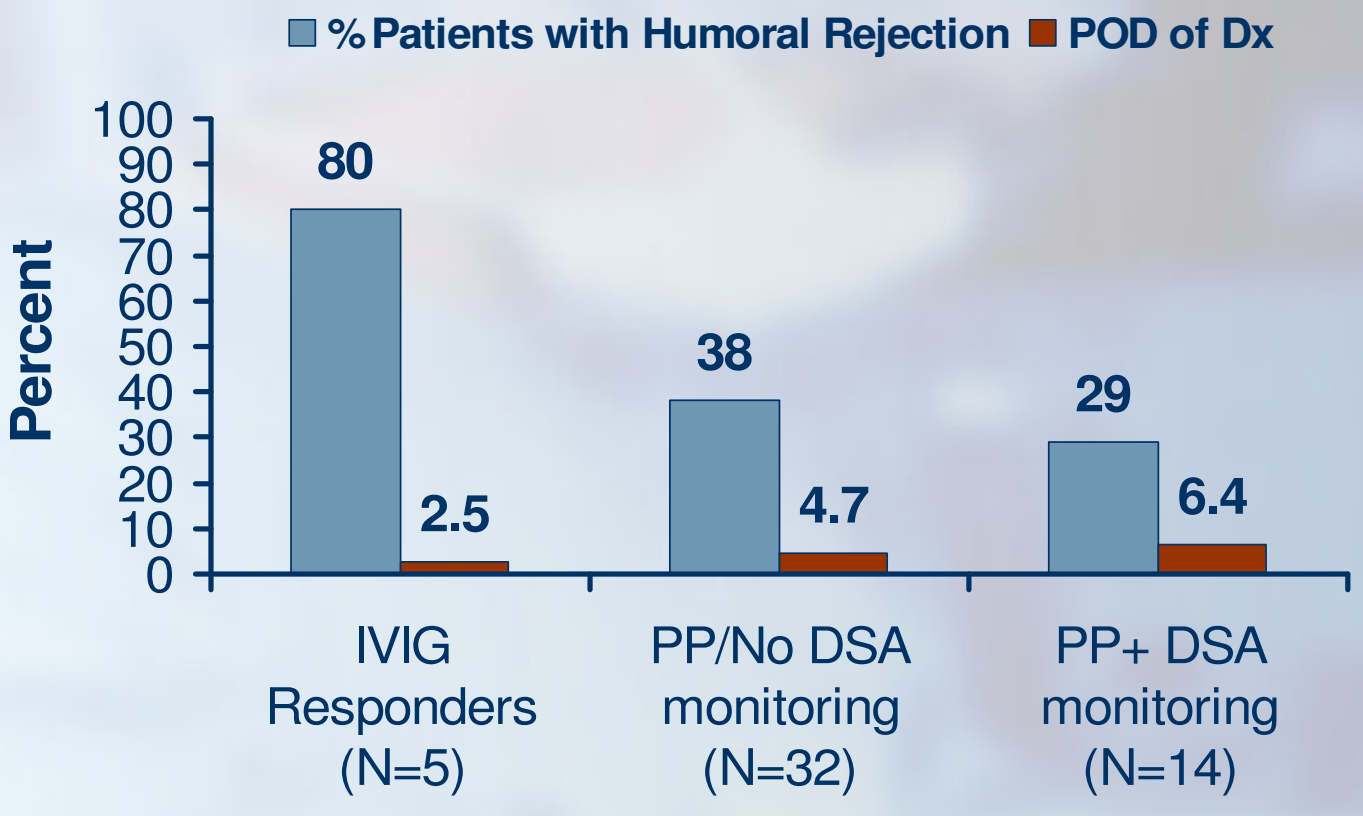
Rejection Rates in 3 Protocols



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IVIG Non-responders Subsequent Response to PP

- Responded
  - 8, 16, 256*
- Remained Positive
  - 8, 16, 32, 32, 128

*Lost graft to humoral rejection

Minimum of 5 PP treatments

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Why a negative T cell AHG Xmatch?

- "Recalcitrant" high titer +XM
- N=10 transplanted with + T cell AHG CDC crossmatch (titer undilute-1:8)
- Humoral rejection 7/10 (70%)
- Allograft loss 5/10 (50%)

Very high rate of HR if CDC XM + at time of transplant

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Overall

- 1 year actuarial results
- Patient survival = 96%
- Graft survival = 84%

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Conclusions: Desensitization

Response correlates with DSA titer

- AHG ≤ 1:4 level DSA patients desensitized with IVIG or PP
- Titers >1:16 difficult to desensitize
- PP more reproducible in intermediate titers

Role of anti-CD20, splenectomy and Thymoglobulin still unclear

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Conclusions: Humoral Rejection

- Unacceptably high in patients with +AHG at time of transplant
- Incidence increases with baseline AHG titer
- Incidence higher with IVIG vs. PP
- ?intensive monitoring delays the onset of post-transplant humoral rejection but does not significantly reduces its incidence

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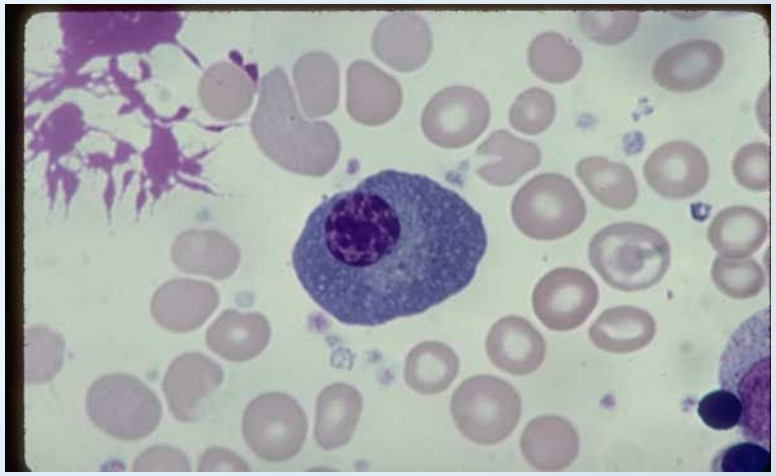
Conclusions

- IVIG vs. PP?
- Lack of control over antibody-producing plasma cells is still a major problem and should be a focus of further research



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