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Depletion therapies in late period antibody-mediated rejection

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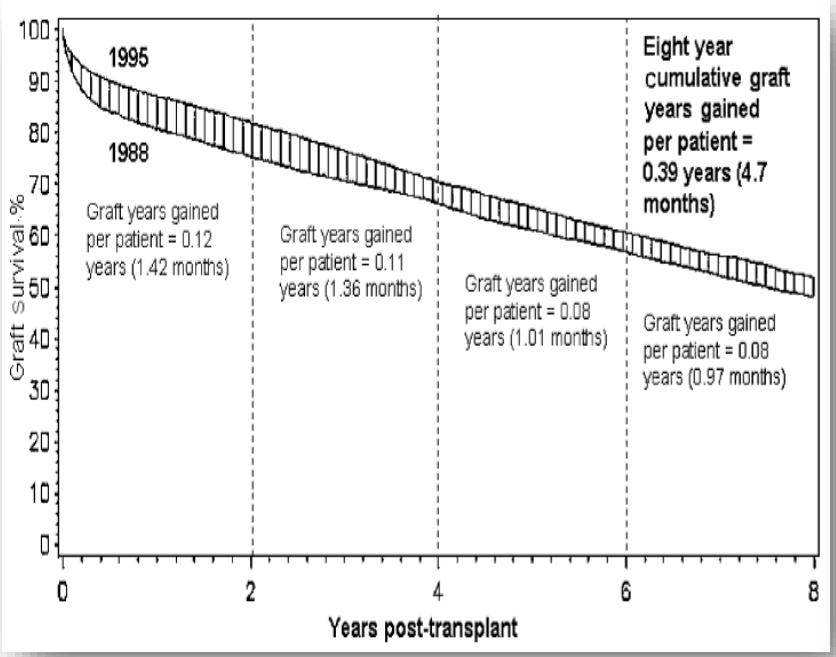
Background: Late period antibody-mediated rejection



Meier-Kriesche H-U et al. Am. J. Transplantation 2004;4:1289-1295

Banff Category	No features of humoral injury	Features of humoral injury	Total
IFTA/CAN	22 (59%)	15 (41%)	37
Rejection	81 (60%)	51 (40%)	132
Idiopathic	6 (86%)	1 (14%)	7
CNI	35 (81%)	8 (19%)	43
Reflux	12 (67%)	6 (33%)	18
Glomerular disease	6 (46%)	7 (54%)	13
Total	162	88 (35%)	250

Saffer S. MMed thesis. Data presented at WCN 2015 and SATS 2015

Reference	N	% of biopsies with ABMR
Einecke G et al Am. J. Transplant 2009;9:2520-2531	27	C4d+ ABMR: 26% All ABMR: 63%
Regele H et al. J. Am. Soc. Nephrol 2002;13:2371-2380	213	C4d+ ABMR: 34%
Matas AJ et al. Am. J. Transplant 2010;10:315-323	240	C4d+ ABMR: 38% DSA+: 40%

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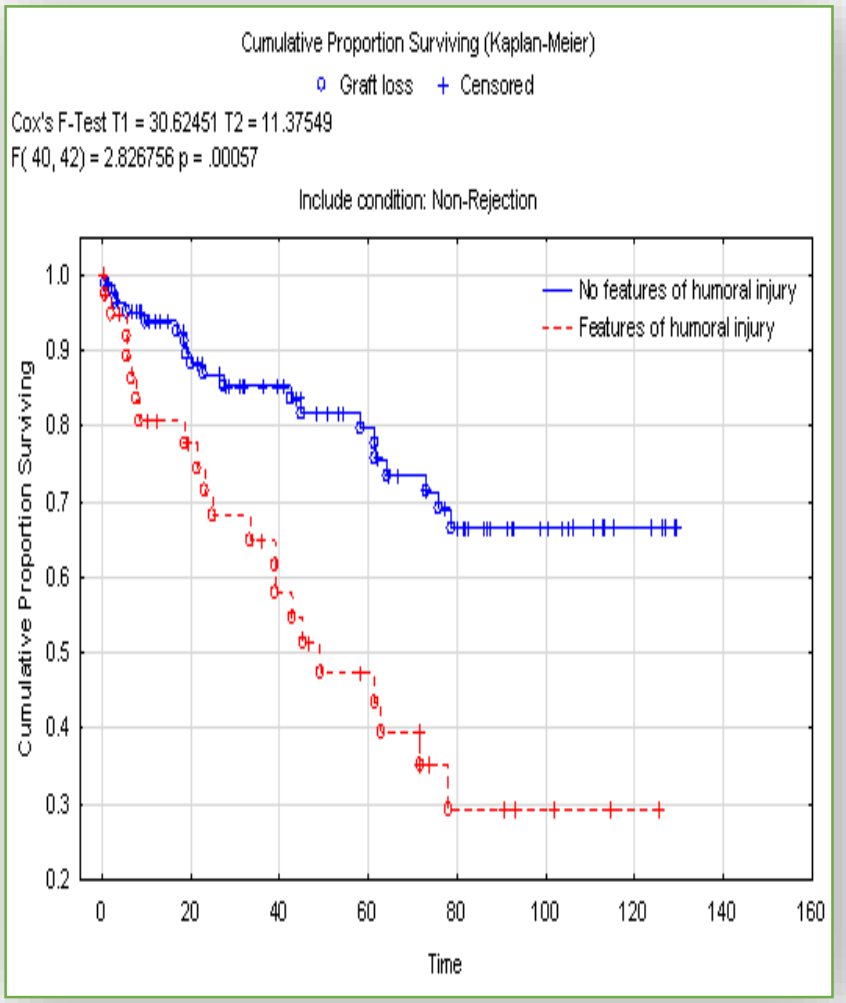
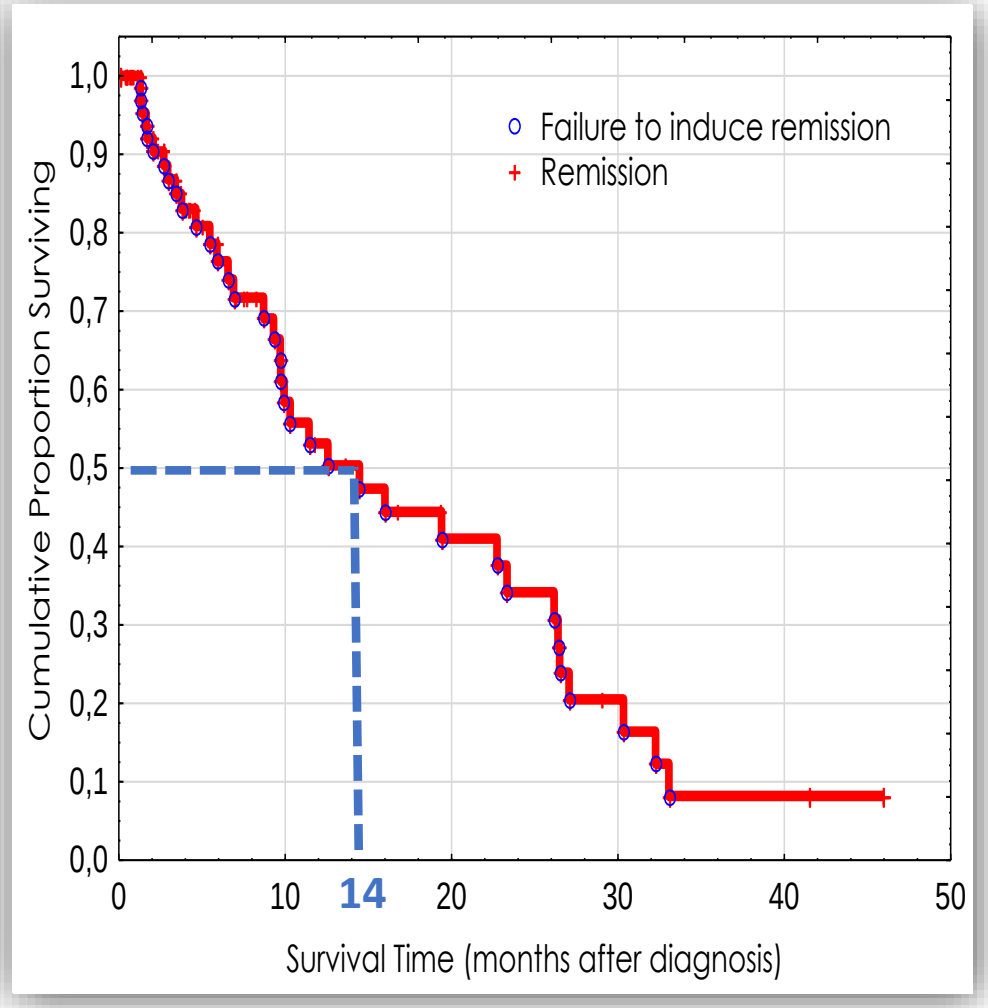
Background: outcome of LPABMR





Saffer S. MMed thesis. Data presented at WCN 2015 and SATS 2015

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Background: management of LPABMR

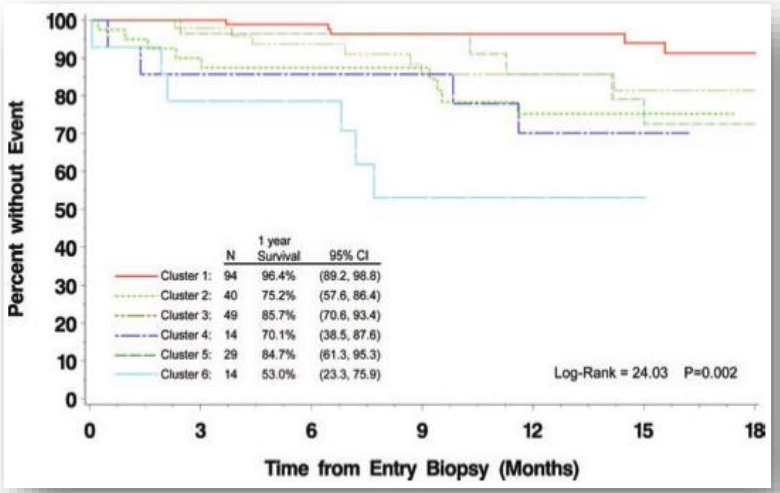
"Currently, there are no FDA-approved treatments for desensitization, and very few randomized controlled trials have been conducted in this area to date"

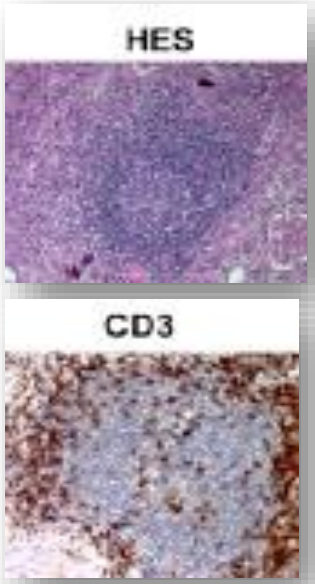
Target	Treatment	Remarks
Antibody removal and immunomodulation	Plasmapheresis IVIg IdeS	Efficacy may be limited in patients with high antibody titres. Effect may be inconsistent depending on DSA specificity Potential for massive proteinuria caused by IgG fragments DSA rebound occurs after Rx
B cells	Rituximab (antiCD20) Belimumab (BAFFi)	Added benefit to SOC (PLEX + IVIg) has not been demonstrated
T cells	ATG	T cells are important in B cell activation Recommended in ABMR with a TCMR component
	Corticosteroids Belatacept (costimulation block)	
Plasma cells	Bortezomib, Carlizomib (proteasome inhibitor) Tocilizumab (IL-6 Ra)	Added benefit to SOC has not been demonstrated, significant toxicitiy Under investigation
Complement	C1 esterase inhibitor C5 inhibitor (eculizumab)	Antibody-mediated damage is not limited to complement-dependent mechanisms; inhibition may not always be effective

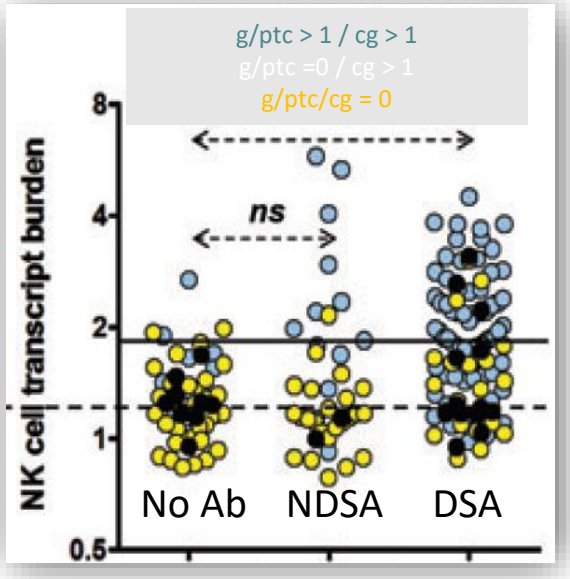
Velidedeoglu E et al. Transplantation 2018;102:e257-e264

Background: potential effect of ATG in LPABMR

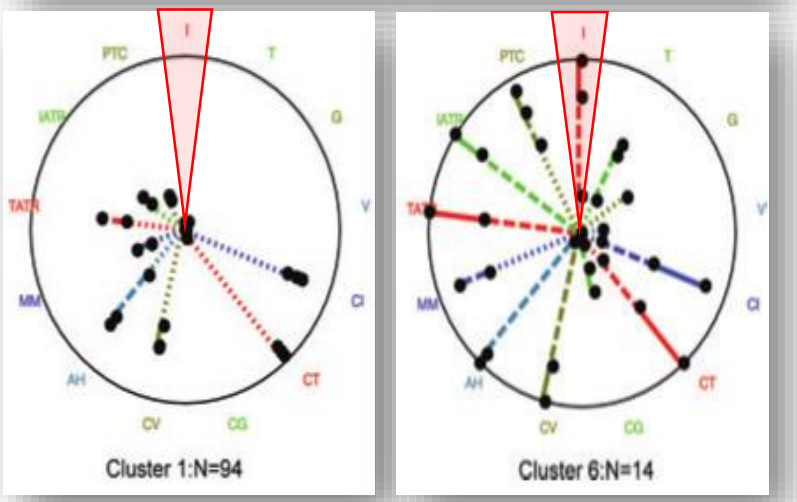
Thaunat O et al. J. Immunol 2010;185:717-728



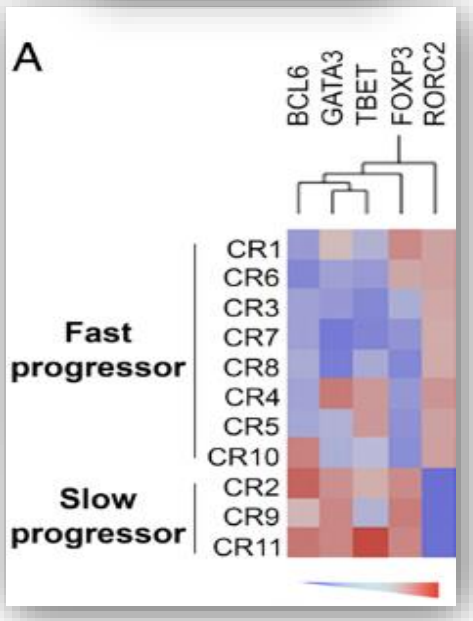




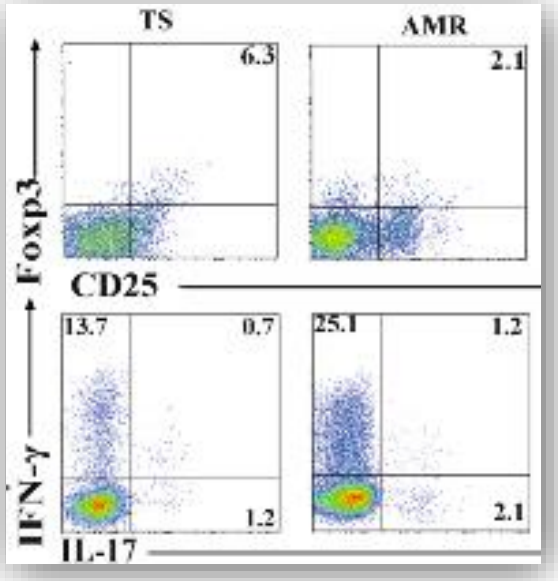
Hidalgo LG et al. Am J Transplant 2012;12:1180-1191



Matas AJ et al. Am J Transplant 2010;10:315-323



Deteix C et al. J Immunol 2010;184:5344-5351



Ma L et al. BMC Immunol 2015;16:56-68

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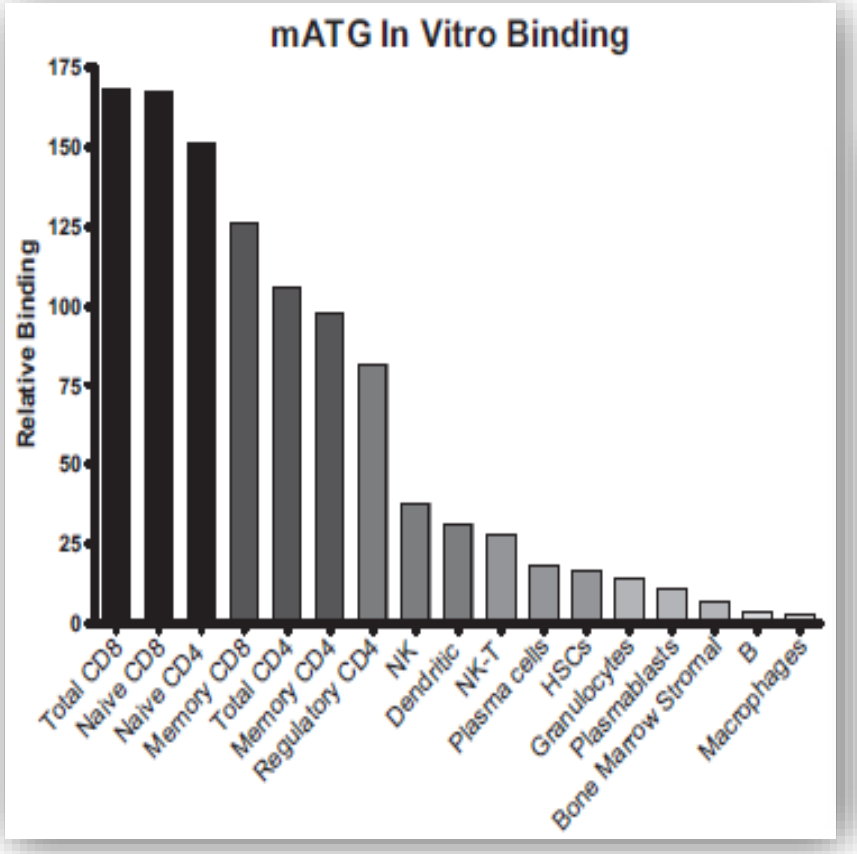
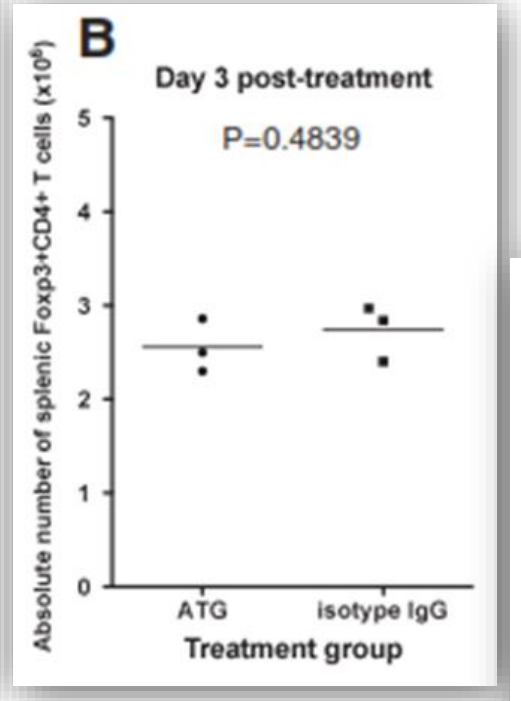
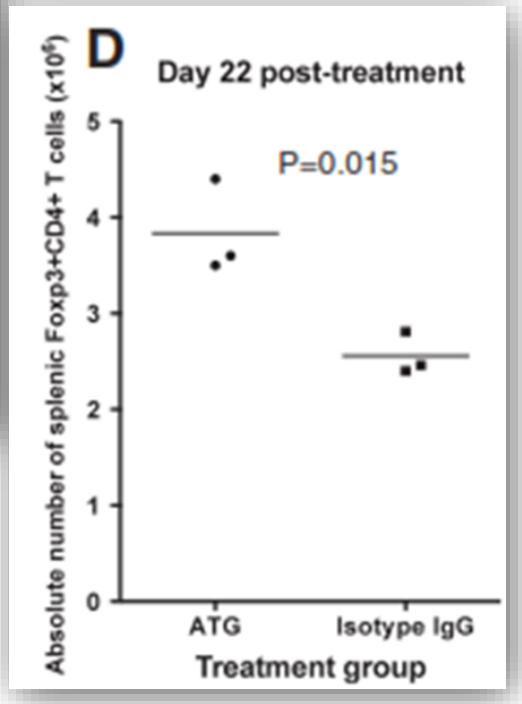
Background: potential effects of ATG in LPABMR



Stauch D et al. PloS ONE 2009;4:e4709





Xia C-Qet al. BMC Immunol 2012;13:70-83

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Background: summary

- Antibody-mediated rejection is a leading cause of late period graft dysfunction and loss
- No consensus exists on the optimal treatment of LPABMR

- Physiologically, control of antibody-mediated injury requires:
  - Depletion of B-cell arm (direct / indirect) - ? validity of targeting CD20+
  - Depletion of T-cell effector arm
- (r)ATG offers the possibility of depleting:
  - B-cell arm (directly via CD138 / CD20; indirectly via CD4)
  - T-cell arm (effector NK / CD8)
- In addition to physiological considerations:

Therapy	Cost /mg*	Dose	Suggested dose**	Cost / dose†	Cost / course††
rATG	ZAR 49.70	1.5mg / kg	1.5 x 70 = 105mg	ZAR 5218.50	ZAR 36526.50
Rituximab	ZAR 69.23	375mg / m^2	375 x 1.7 = 637.50mg	ZAR 44134.13	ZAR 176536.52

*South African Medicine Price Registry accessed from http://mpr.gov.za 25/8/2019

**Suggested dose assumes average weight of 70kg and average body surface area of 1.7m^2

†Cost / dose= (cost/mg) x (total dose)

††Cost / course = (cost / dose) x (4 for RTX, 7 for ATG)

Methods

- A retrospective subanalysis of the CMJAH LPABMR cohort was conducted
  - Patients receiving PLEX + IVIg followed by depletion therapy (RTX / ATG) were included (n = 34)

- Baseline characteristics were compared between RTX and ATG treatment arms
  - Logistic regression was used to retrospectively compare potential indications for ATG prescription over RTX

- Clinical remission (stabilization of graft function) was compared between RTX and ATG groups

Results: prescription of ATG vs RTX

	RTX (n=23, 67.6%)	ATG (n = 11, 32.3%)	p
Number of detected specificities			
HLA-A	1 (0 – 4)*	0 (0 – 8)	0.837
HLA-B	0 (0 – 2)	0 (0 – 1)	0.490
HLA-DQA	0 (0 – 1)	1 (0 – 6)	0.447
HLA-DQB	5 (2 – 7)	5 (0 – 7)	0.837
MFI of detected specificities			
HLA-A	0 (0 – 3495)	0 (0 – 2882)	0.817
HLA-B	0 (0 – 1132)	0 (0 – 1085)	0.585
HLA-DQA	0 (0 – 15740)	1988 (0 – 16312)	0.581
HLA-DQB	6995 (1564 – 18749)	3042 (0 – 16312)	0.535
Graft age at diagnosis (months)	177 (136 – 330)	56.8 (30.1 – 170.03)	0.188
Creatinine at diagnosis (mmol/L)	**106.3 (74.7 – 177.8)**	**358 (271 – 454)**	**0.003**
IFTA grade	0: 14% 1: 57% 2: 29% 3: 0%	0: 13% 1: 38% 2: 38% 3: 13%	0.359**
i-score	0: 38% 1: 33% 2: 14% 3: 14%	0: 25% 1: 13% 2: 50% 3: 13%	0.233**

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Results: factors determining creatinine

Predictor		b	SE b	F	df	p
cg-score Dx Bx:	0	-0.0304	0.1938	0.2682	3	0.876
	1	-0.1382	0.2133			0.520
	2	0.0387	0.2237			0.863
IFTA grade Dx Bx:	0	0.0157	0.1391	0.3915	3	0.911
	1	-0.0095	0.1593			0.952
	2	-0.1707	0.1613			0.296
i-score Dx Bx:	0	-0.1988	0.1541	2.8015	3	0.203
	1	-0.1822	0.1576			0.254
	2	**0.4293**	**0.1567**			**0.008**

Results: factors determining ATG prescription

Predictor		β	SE β	Wald's χ^2	df	p
Creatinine at Dx		0.0033	0.0022	2.1023	1	0.147
DQ MFI		-0.0000	0.00004	0.0001	1	0.991
Mixed rejection Dx Bx		**0.6118**	**0.3339**	**3.3577**	1	**0.067**
cg-score Dx Bx:	0	-9.2667	107.0752	0.0075	3	0.931
	1	-15.2766	234.7290	0.0042		0.948
	2	12.9107	132.1529	0.0264		0.922
IFTA grade Dx Bx:	0	**1.6033**	**0.8868**	**3.2691**	3	**0.071**
	1	**-1.1792**	**0.6673**	**3.1228**		**0.077**
	2	-0.2972	0.7402	0.1611		0.688
i-score Dx Bx:	0	-0.0054	0.5384	0.0001	3	0.992
	1	-1.421	0.8498	2.799		0.094
	2	**1.551**	**0.772**	**4.030**		**0.044**

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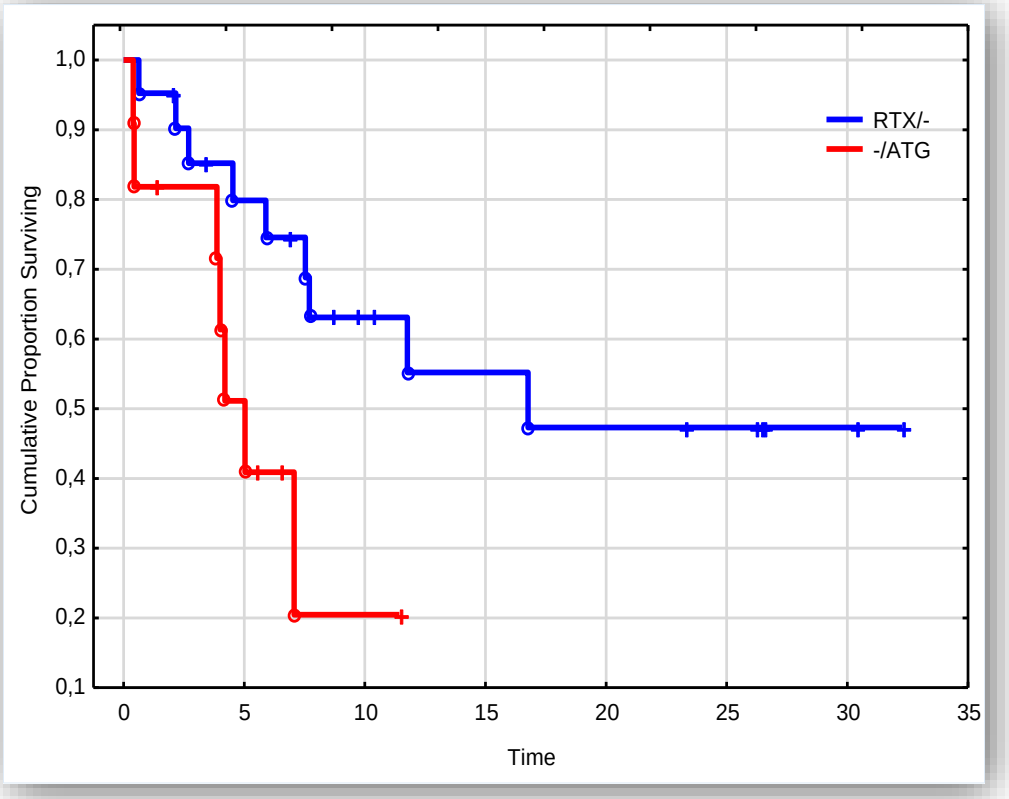
Results: poorer outcomes with ATG



Cox Mantel
F = 2.28,
p = 0.023

Predictor	β	SE β	Wald's χ^2	df	p	HR (95% CI)
RTX	-0.5007	0.3015	2.758	1	0.097	0.367 (0.113 – 1.198)
ATG	0.4770	0.4600	1.4350	1	0.231	3.250 (0.591 – 22.825)

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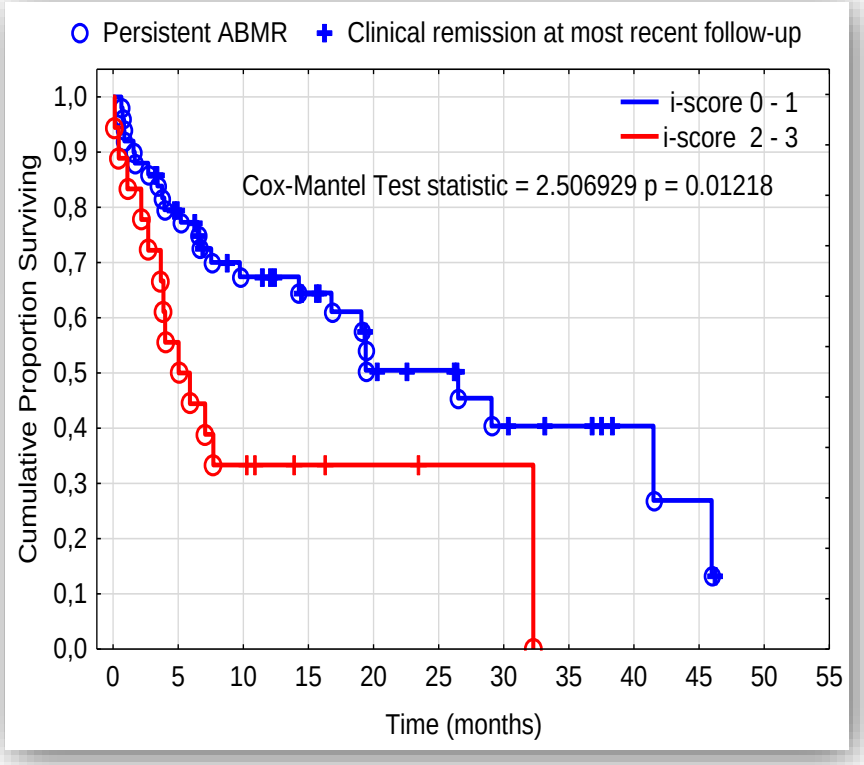
Results: i-score and outcome

Predictor	β	p	HR
Mixed Rejection	0.3304	0.2375	1.936
IFTA grade:			
0	-0.6527	0.0980	0.1336
1	-0.7074	0.2480	0.1149
≥ 2	-0.0958	0.8055	0.2119
i-score:			
0	-0.5865	0.3297	0.251
1	-0.2064	0.7501	0.932
≥ 2	**1.3320**	**0.0210**	**2.640**



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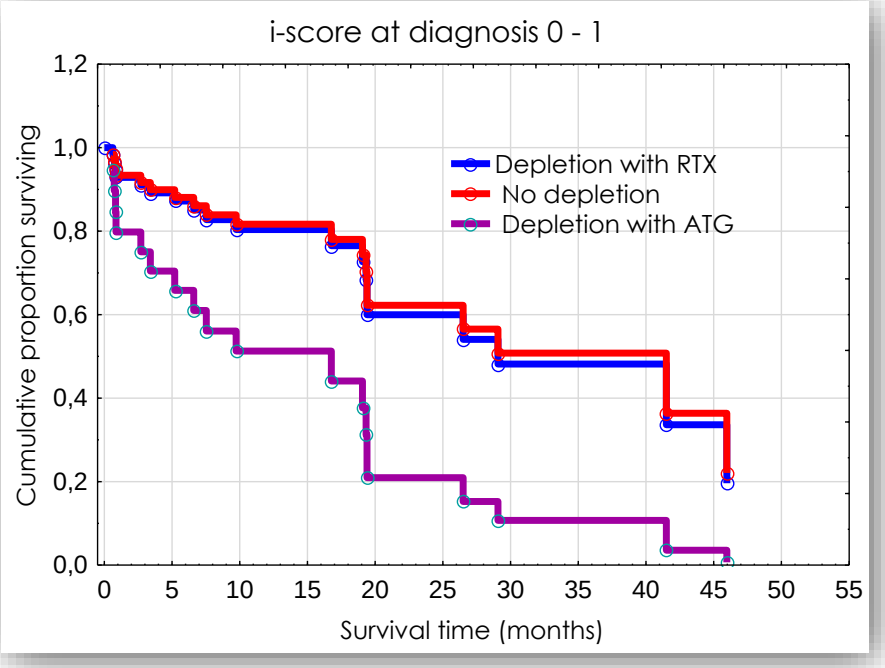

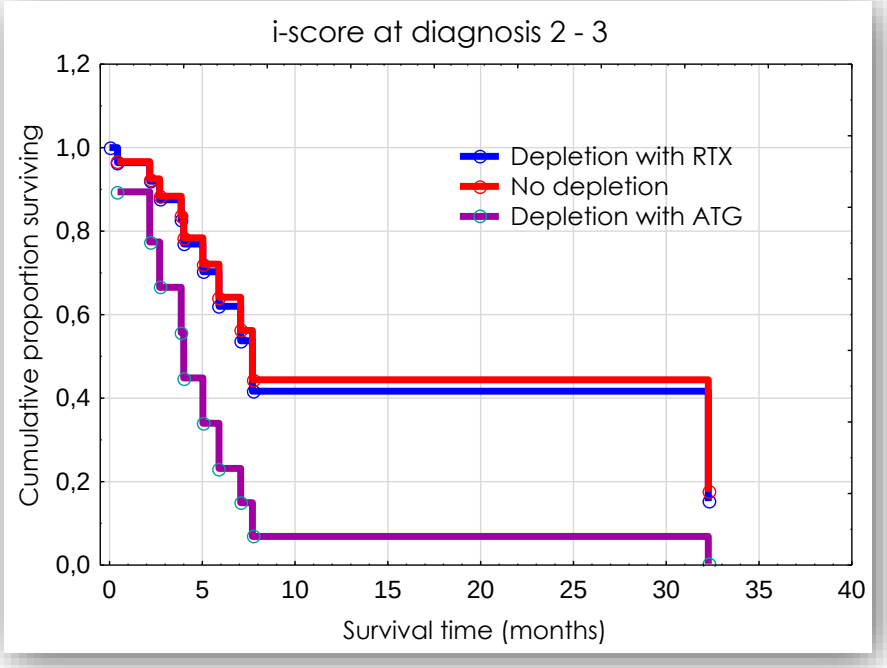

Predictor	β	SE β	Wald's χ^2	p	Hazard ratio (95% CI)
Rituxmab	-0.3476	0.2855	1.4826	0.2233	1.0781 (0.4044 – 2.8742)
ATG	0.7705	0.3226	5.7032	0.0169	3.2980 (1.0920 – 9.9607)

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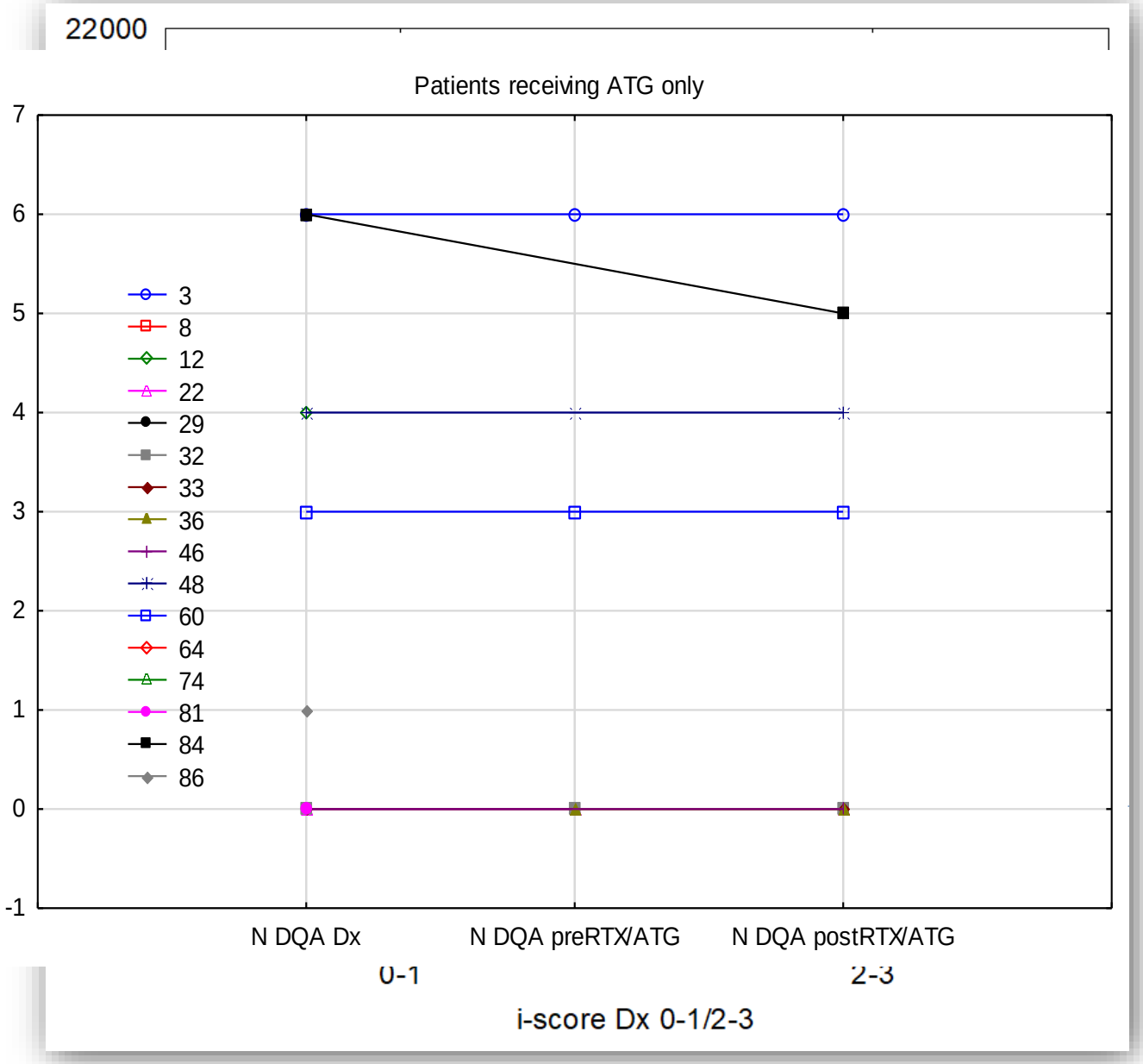
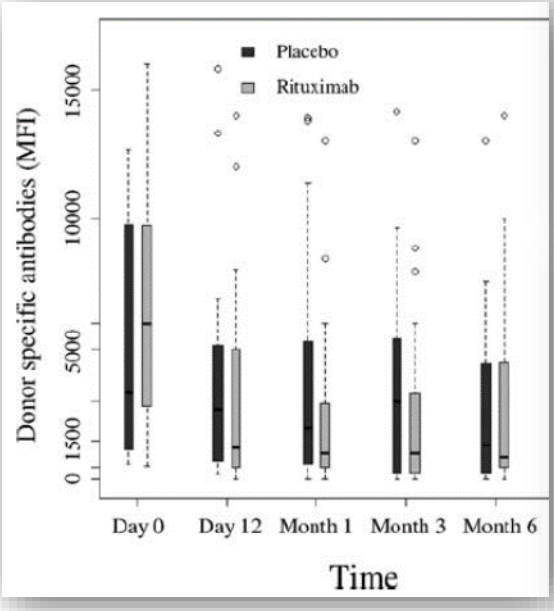
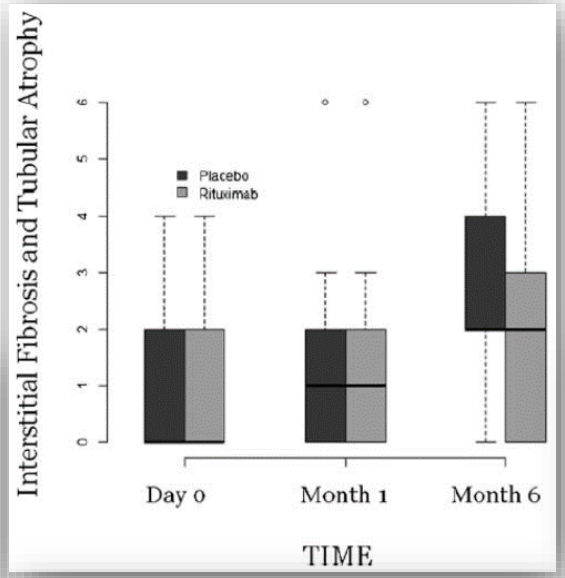
Results: DSA response to ATG

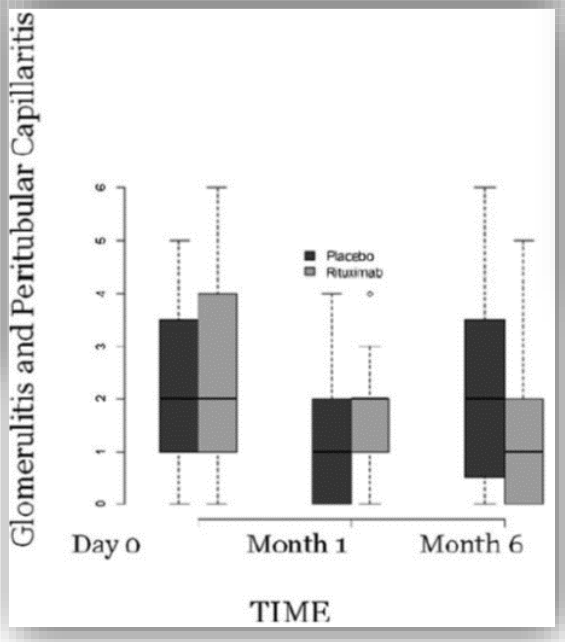
- MFI A Dx
- MFI B Dx
- MFI DQA Dx
- MFI DQB Dx
- MFI A preRTX/ATG
- MFI B preRTX/ATG
- MFI DQA preRTX/ATG
- MFI DQB preRTX/ATG
- MFI A postRTX/ATG
- MFI B postRTX/ATG
- MFI DQA postRTX/ATG
- MFI DQB postRTX/ATG

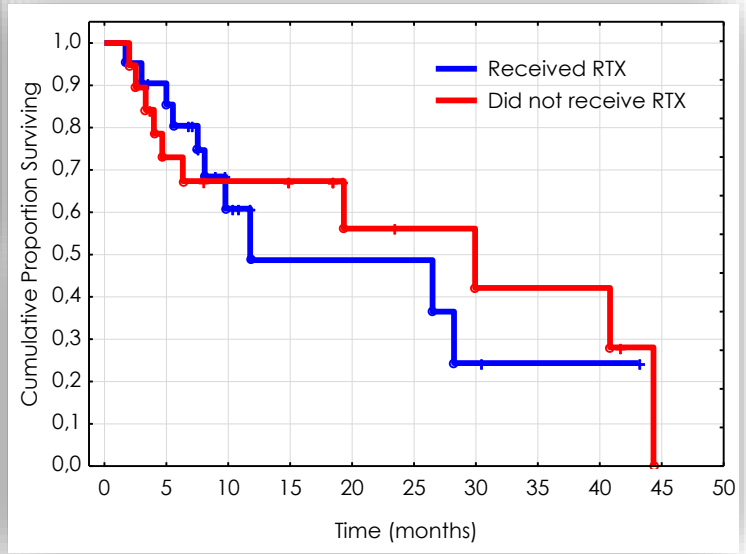


Discussion: RTX is of dubious benefit in ABMR









Cox F = 1.35, p = 0.390

Sautenent B et al. Transplantation 2016;100:391-399

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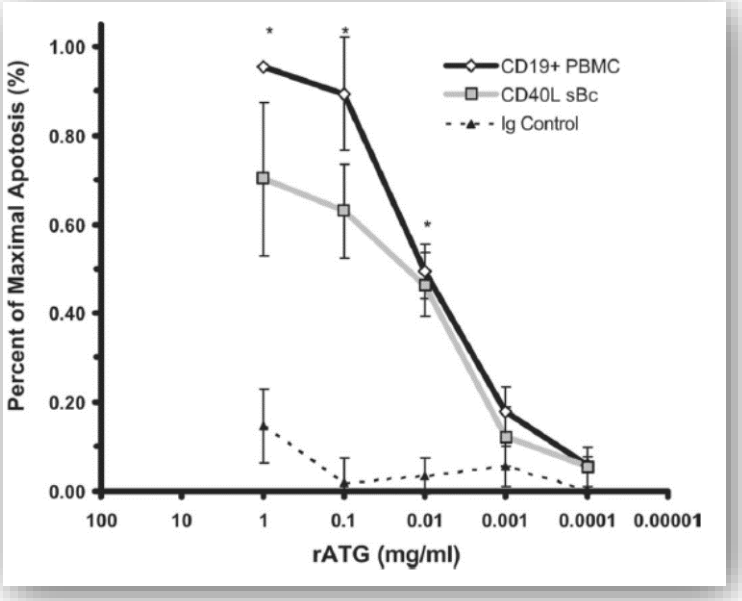
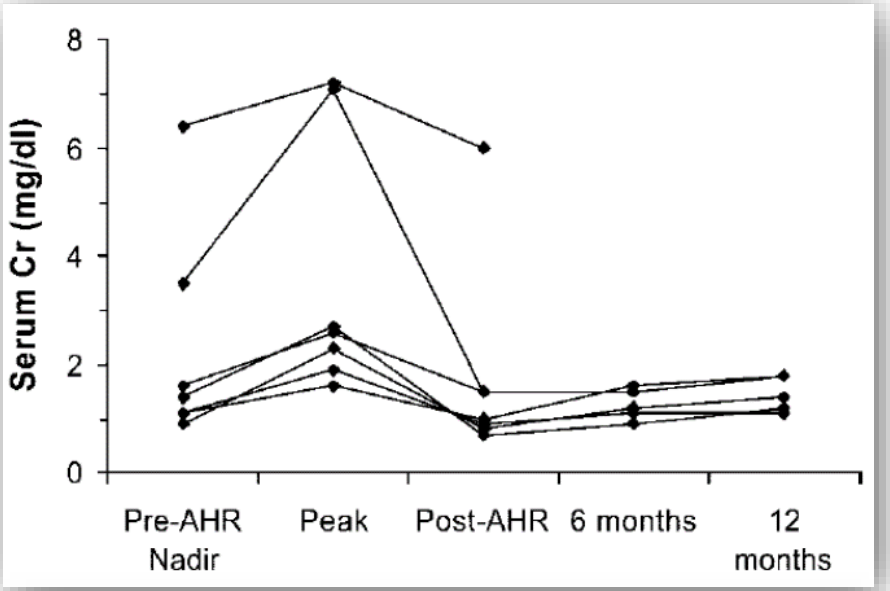
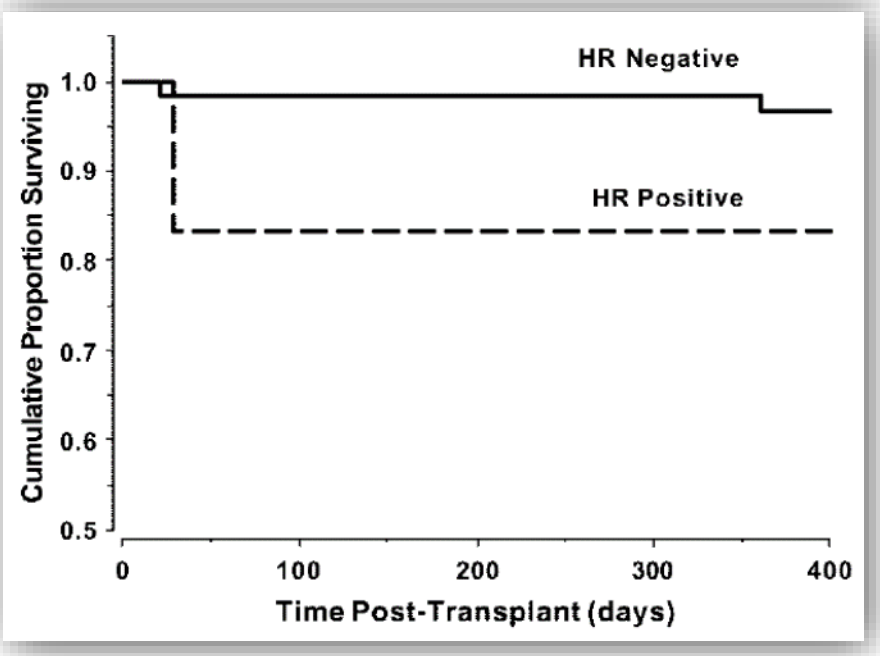
Discussion: evidence for ATG in ABMR is poor



Shah A et al. Transplantation 2004;77:1399-1405





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Discussion: ATG may precipitate ABMR

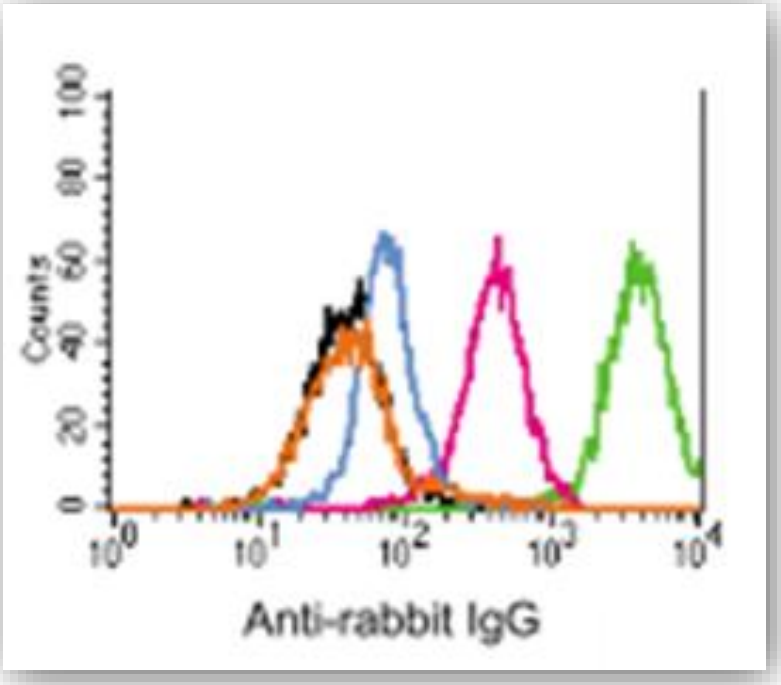
TABLE 2 Posttransplant antibody status of all subjects

	ATG (n = 27)	No ATG (n = 27)	*p* value
Increase in HLA-Ab >10% posttransplant	**6 (22.2)**	**1 (3.7)**	**0.05**
Class I	6 (22.2)	0 (0.0)	**0.023**
Class II	2 (7.4)	1 (3.7)	NS
Any increase in HLA-Ab	10 (37.1)	3 (11.1)	**0.026**
Any increase Class I HLA-Ab	6 (22.2)	2 (7.41)	0.125
Any increase Class II HLA-Ab	6 (22.2)	1 (3.7)	**0.05**
PRA (% ± SD)	36.5 ± 54.7	10.3 ± 20.3	0.16
Class I	16.3 ± 29.0	6.7 ± 12.1	NS
Class II	20.2 ± 29.4	3.6 ± 11.6	**0.012**

Tinckam KJ et al. Human Immunol 2004: 1281-1287

Negative control

ATG (micg/ml): **0.05** **0.5** **5** **50**



Colovai AI et al. Human Immunol 2005;66:501-512

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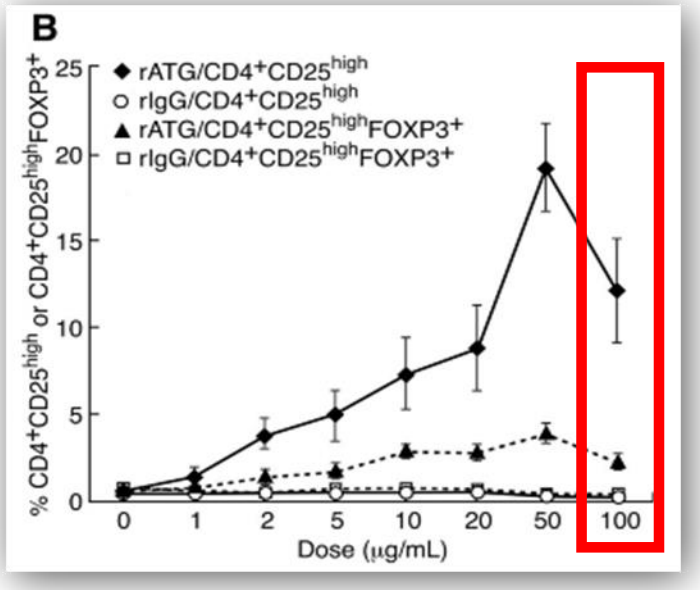
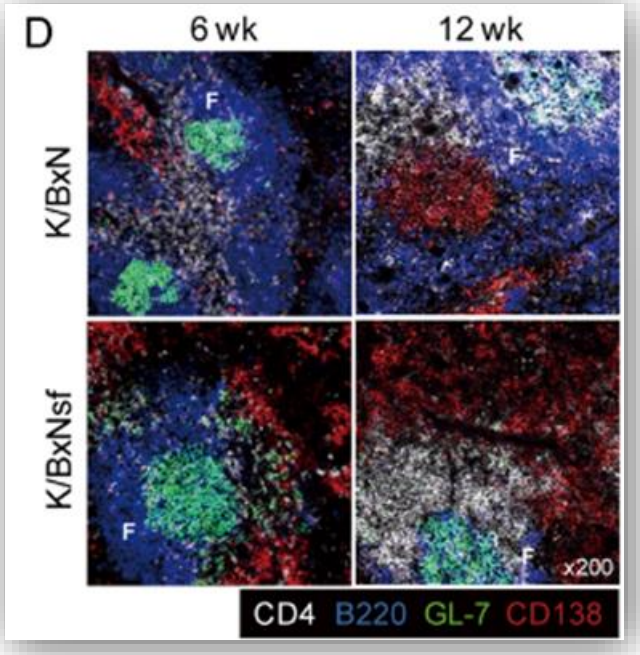
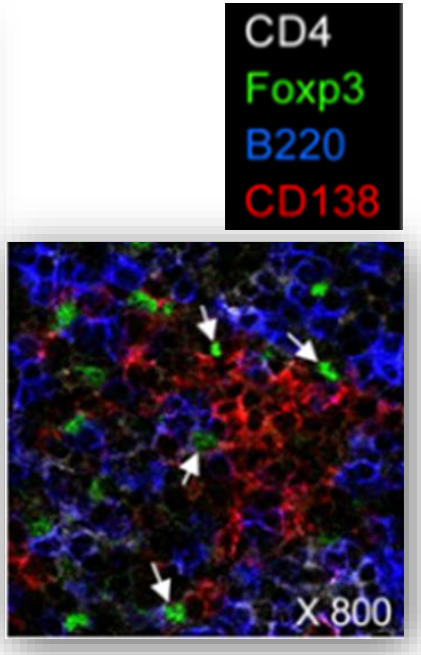
Discussion: ATG may worsen loss of tolerance



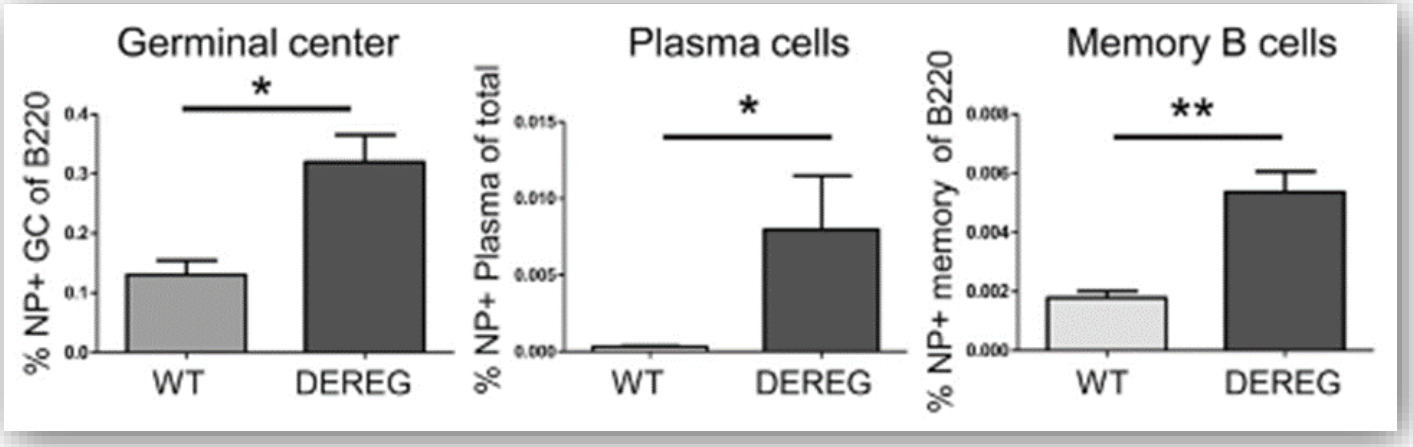
Feng X et al. Blood 2008;111:3675-3683





Wing JB et al. Immunity 2014;41:1013-1025

Jang E et al. J Immunol 2011;186:1546-1553



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Conclusions

- ABMR is an important cause of late period graft dysfunction and loss
- Consensus on treatment of LPABMR is lacking
- Despite initial enthusiasm current data does not support the efficacy of RTX in the treatment of LPABMR
- i-score is predictive of graft loss; ATG has been suggested as a potential therapy in LPABMR with significant interstitial infiltrate / mixed rejection
- Evaluation of the CMJAH cohort suggests that ATG may accelerate graft loss in LPABMR
- Loss of Treg-mediated dampening of long-lived plasma cell clones responsible for DSA production may underlie this observation

Acknowledgements

- Dr F Khan, Dr S Saffer
- Dr P Mosiane, Prof S Goetsch
- Ms C Worsely, Dr M Suchard