Minimisation of immunosuppression: Necessary or Necessity?

Jack Galliford

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West London Renal and Transplant Centre
Imperial College Renal and Transplant Centre
Hammersmith Hospital
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Kidney and Transplant Centre

Imperial College Renal and Transplant Centre

The amalgamation of 3 renal units in 2005

- St Mary's Hospital, Paddington
- Charing Cross Hospital, Hammersmith
- Hammersmith Hospital, East Acton

One site chosen

'Critical Mass'

Serve a population of 3 million

Purpose built facility

2 x HDU's [15 beds]

3 wards [60 beds]

1 x 16 bedded Programmed Investigation Unit

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Activity:

160-170 Renal Transplants annually

[50% live donor transplants]

10-15 Pancreatic Transplants annually

Over 1500 transplant follow up patients

1500 Dialysis patients

8 Satellite hospitals

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Talk outline

Brief literature review

Local data

Steroids

Campath/ Alemtuzumab

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Steroids

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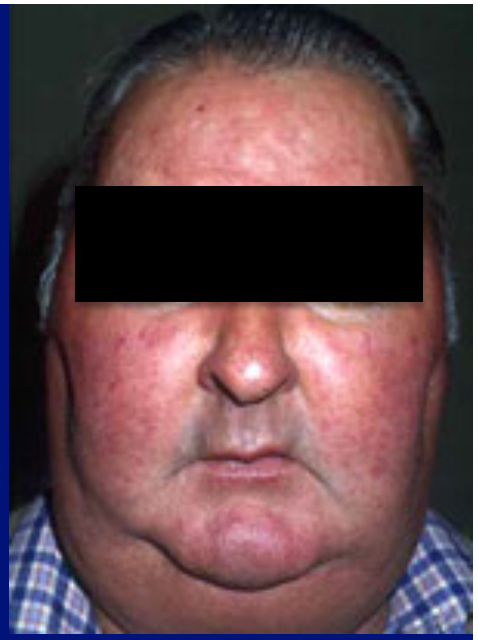
History



The morbidities induced by steroids are huge

Elimination of steroid use has failed

Any success in reducing exposure has been limited by a fear of
Increased acute rejection and late allograft loss

Sinclair NR et al Can Med Assoc J. 1992; 147: 645
8% in a Canadian Study [small but multicentre and double blinded]
The impact of this study cannot be overestimated

History of steroid withdrawal

1990's Corticosteroid Withdrawal [CSWD]
Tacrolimus based immunosuppression
2 centres reported success

1995
FDA approved MMF
Early CSWD using platform of Tac/ MMF [1 week]
1 year AR 21%
Included high risk populations [re-grafts, Afro-Americans, sensitised]

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Renal transplantation without steroids

Why ?

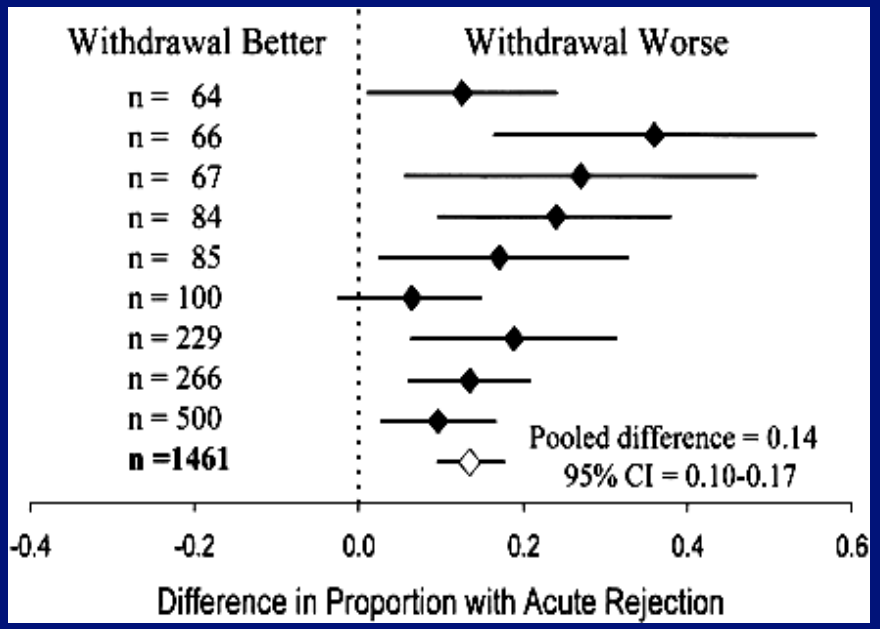
1] Reduce incidence of cardiac and vascular disease

2] Reduce incidence of New Onset Diabetes Mellitus [NODAT]

3] Avoid other steroid induced complications

4] Patient choice

5] Improve compliance



Kasiske, JASN 2001
Steroid withdrawal
RR for graft failure 1.40
[p=0.012]

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A Prospective, Randomized, Double-Blind, Placebo-Controlled Multicenter Trial Comparing Early (7 Day) Corticosteroid Cessation Versus Long-Term, Low-Dose Corticosteroid Therapy

E. Steve Woodle, MD, M. Roy First, MD,† John Pirsch, MD,‡ Fuad Shihab, MD,§ A. Osama Gaber, MD,¶ and Paul Van Veldhuisen, PhD,‖ for the Astellas Corticosteroid Withdrawal Study Group*

Until 2008, there was **NO** double blinded evidence to refute the Canadian paper

397 patients

Either Chronic Corticosteroid Therapy [CCT]

Corticosteroid Withdrawal [CSWD]

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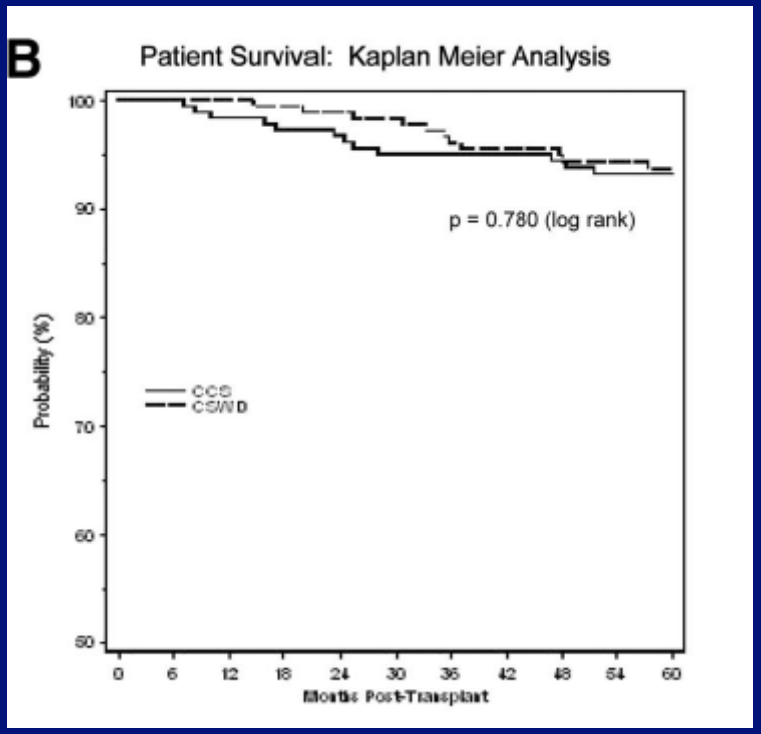
Results



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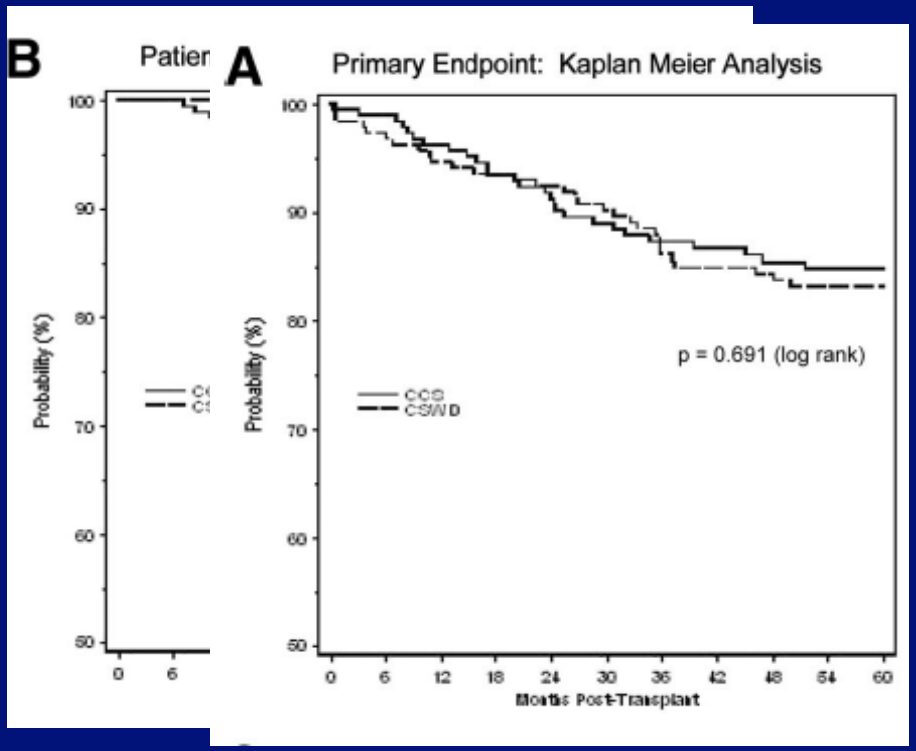
Allograft survival [uncensored]



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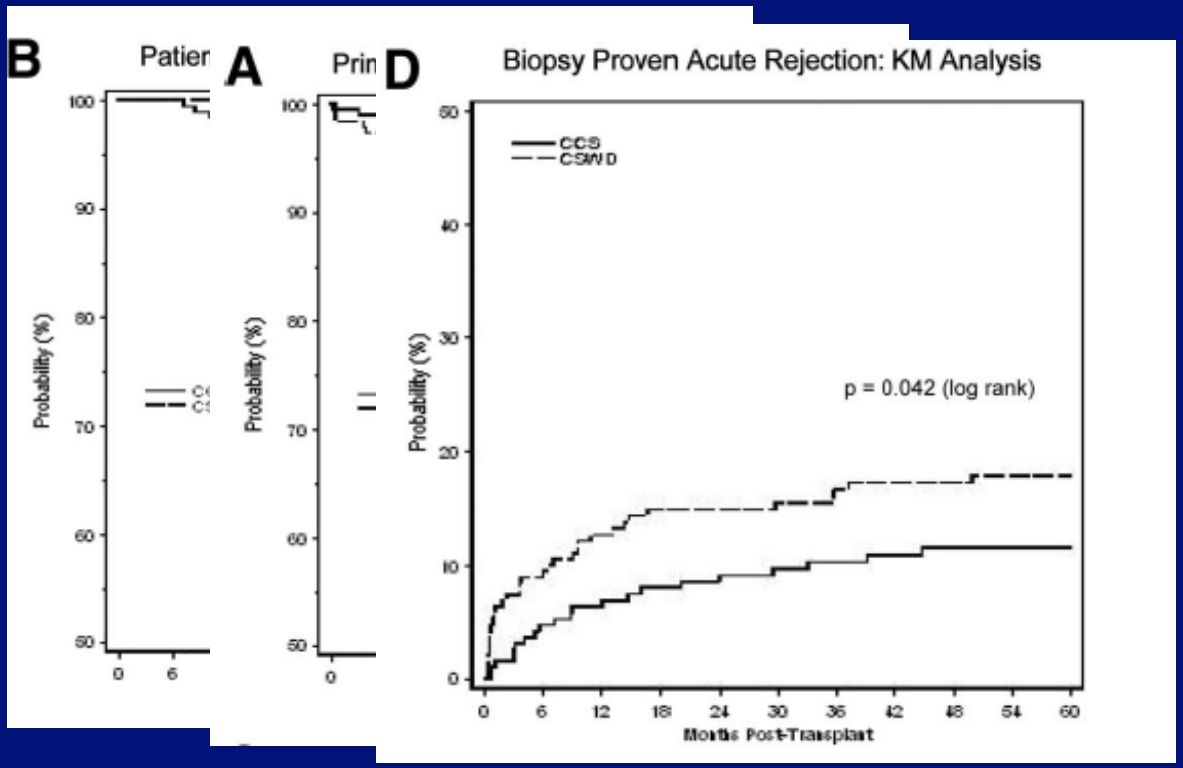
Rejection [1]



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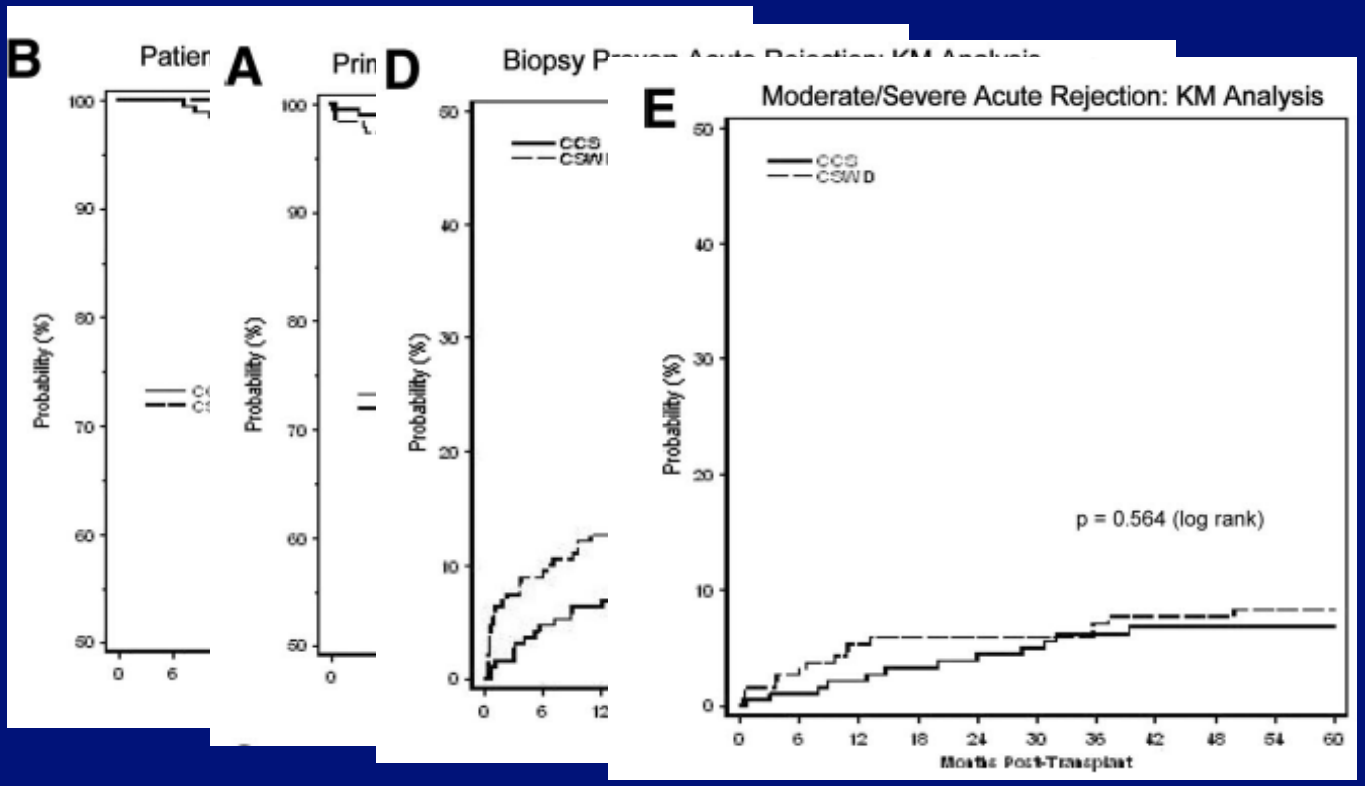
Rejection [2]



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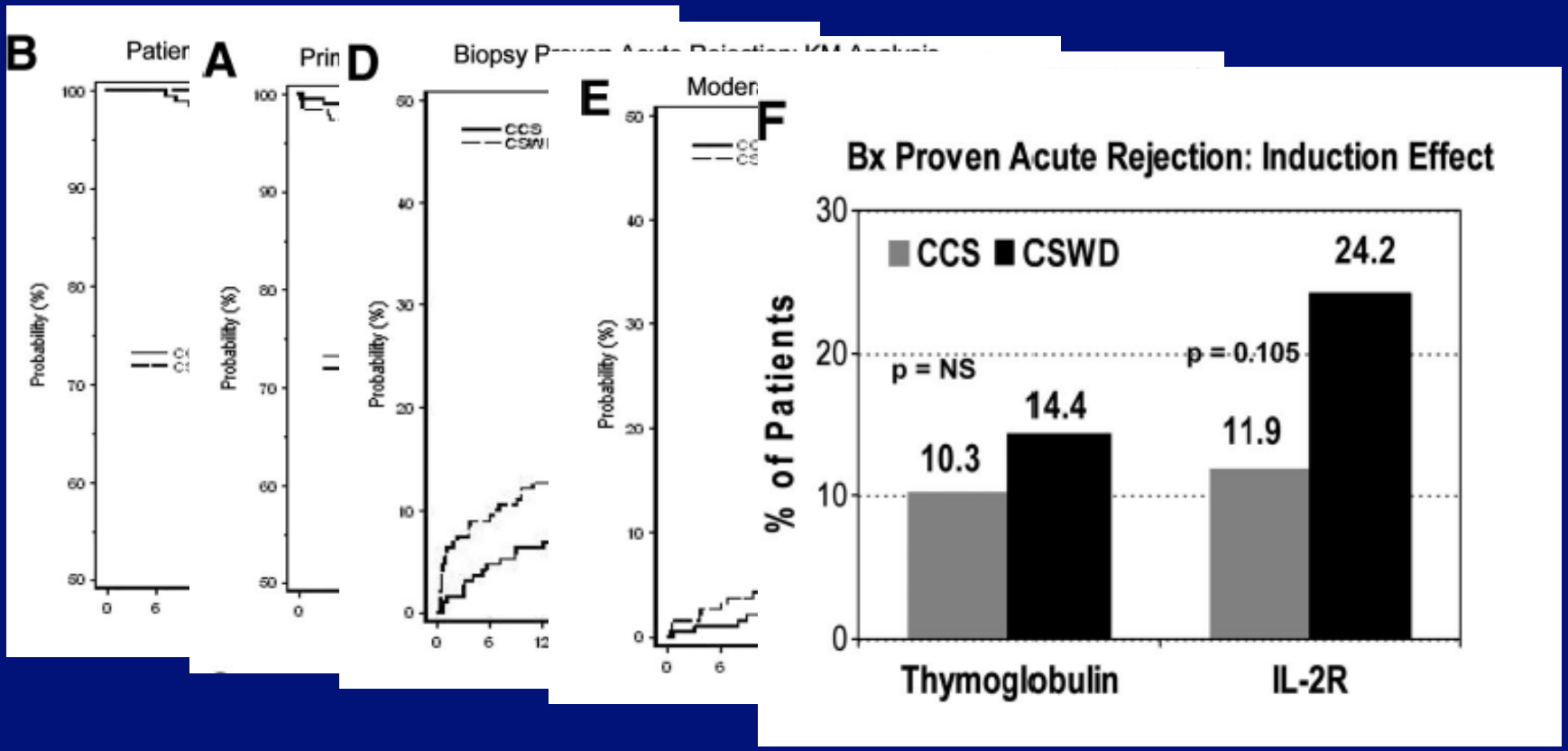
Rejection [3]



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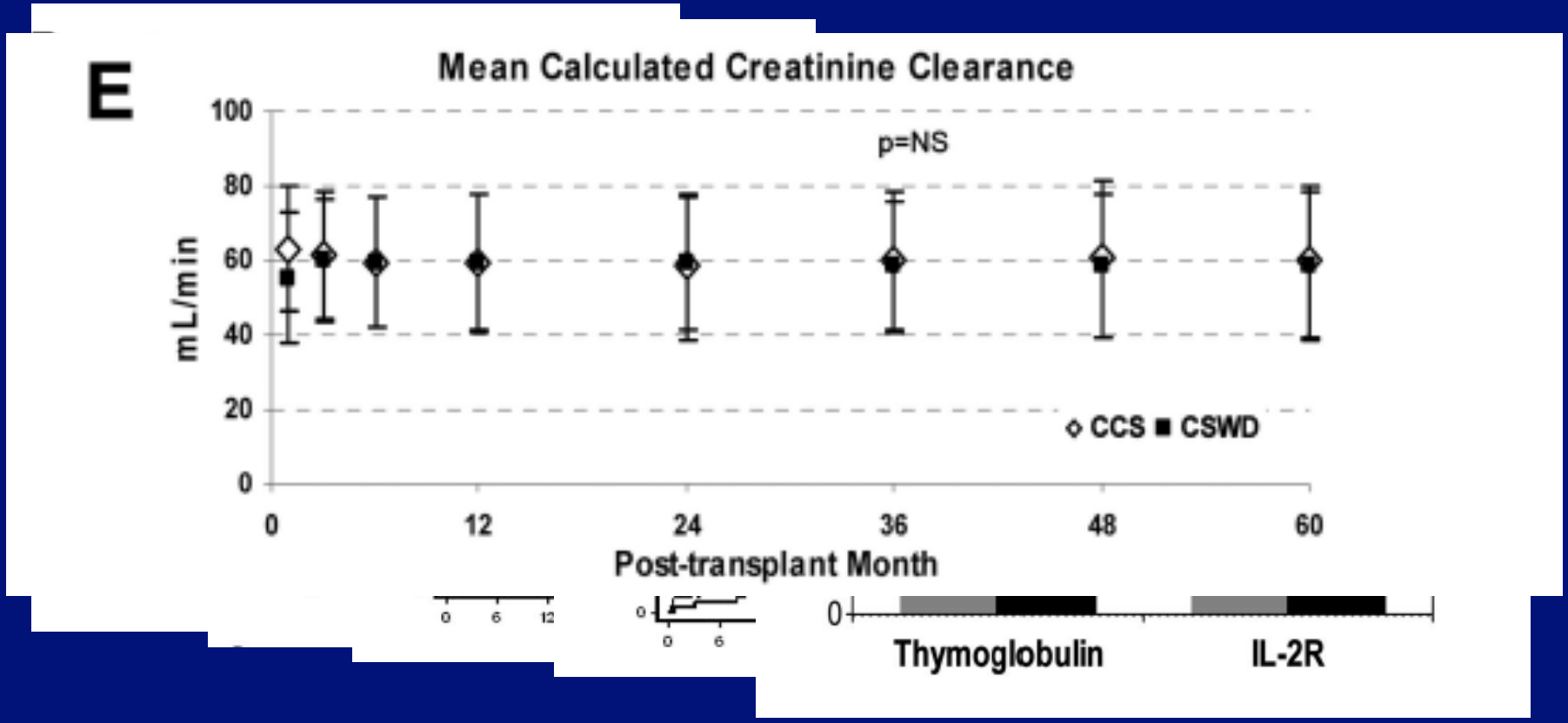
Function



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A Prospective, Randomized, Double-Blind, Placebo-Controlled Multicenter Trial Comparing Early (7 Day) Corticosteroid Cessation Versus Long-Term, Low-Dose Corticosteroid Therapy

E. Steve Woodle, MD, M. Roy First, MD,† John Pirsch, MD,‡ Fuad Shihab, MD,§ A. Osama Gaber, MD,¶ and Paul Van Veldhuisen, PhD,‖ for the Astellas Corticosteroid Withdrawal Study Group*

Conclusion, at 5 years:

[CSWD good]

Less diabetes, fewer infections, less AVN, better weights [short term], better TG's

Safe

[CSWD bad]

No increased Framingham risk, no change in bp, no LDL/ T chol. Difference

No mortality benefit

More rejection

Steroid sparing regimes at Imperial College Renal and Transplant Centre

St Mary's Hospital

1995
Tacrolimus used as CNI

20% incidence of NODAT at 1 year with Tacrolimus, MMF and steroids

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Steroid sparing regimes at Imperial College Renal and Transplant Centre

SMH 2000
20% incidence of NODAT at 1 year with Tacrolimus, MMF and steroids

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Steroid sparing protocols in West London; the last 10 years

2000 – April 2002
Tacrolimus [0.15mgs/kg/day]
Mycophenolate Mofetil 750mg bd
Steroid sparing [0.5 gms methyl prednisolone operatively, then prednisolone 30mg bd day 0-4; 30mg od day 5-7 then stopped]
Antibody induction for high risk recipients

April 2002 – August 2004*
Daclizumab induction day 0 and day 14
Tacrolimus [0.15mgs/kg/day]
Mycophenolate Mofetil 750mg bd
Steroid sparing

August 2004 –
Campath 30 mgs iv peri operatively
Tacrolimus monotherapy [0.1mg/kg/day]
Steroid sparing and no MMF

*Borrows et al, Transplantation 2006

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Demographics

836 patients

		n [%]
Ethnicity	Caucasian	438 [52.4%]
	Afro Caribbean	96 [11.5%]
	Asian	245 [29.3%]
	Other	57 [6.8%]
Gender	F	321 [38.4%]
	M	515 [61.6%]
Type of graft	Deceased donor	435 [52.0%]
	Living donor	401 [48.0%]
Induction	Methyl prednisolone only	85 [10.2%]
	Daclizumab	228 [27.3%]
	Campath	523 [62.6%]
Primary transplant	Y	747 [89.4%]
	N	89 [10.6%]

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Demographics

	mean + 1 SD
Recipient age [Years]	46.7+13.0
Total HLA MM	3.2+1.7
Donor age [Years]	44.9+14.6
Length of stay [Days]	13.6+11.6
Follow up [Months]	35.4+28.1

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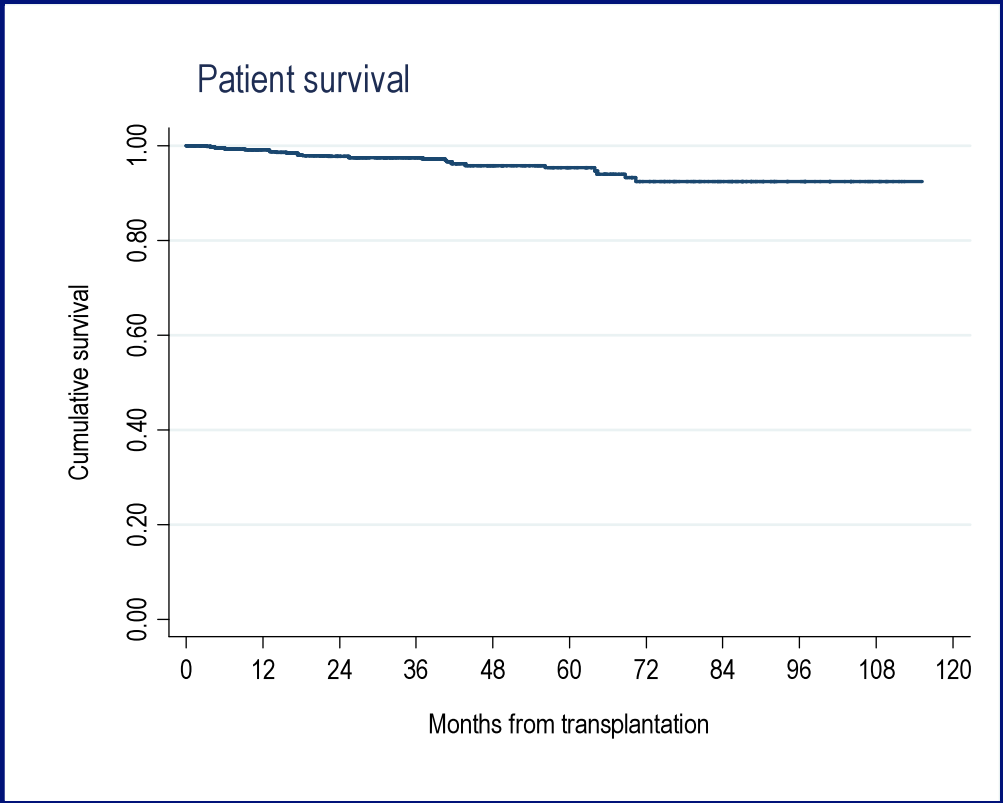
Patient Survival



Month	Cumulative survival	[95% ci]
12	98.9%	[97.8%,99.5%]
36	97.3%	[95.7%,98.4%]
60	95.1%	[92.4%,96.9%]
120	92.3%	[87.9%,95.1%]

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Patient Survival

10 year patient survival is 92%

Causes of death	n [%]
Cardiac	6 [22.2%]
Malignancy	6 [22.2%]
Sepsis	5 [18.5%]
ESP	4 [14.8%]
Sudden death	3 [11.1%]
Aortic Aneurysm	1 [3.7%]
CMV	1 [3.7%]
Hepatic failure	1 [3.7%]

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Allograft survival

Month	Cumulative survival	[95% ci]
12	95.2%	[93.5%,96.5%]
36	90.1%	[87.5%,92.2%]
60	85.4%	[81.8%,88.4%]
120	74.7%	[67.0%,80.8%]

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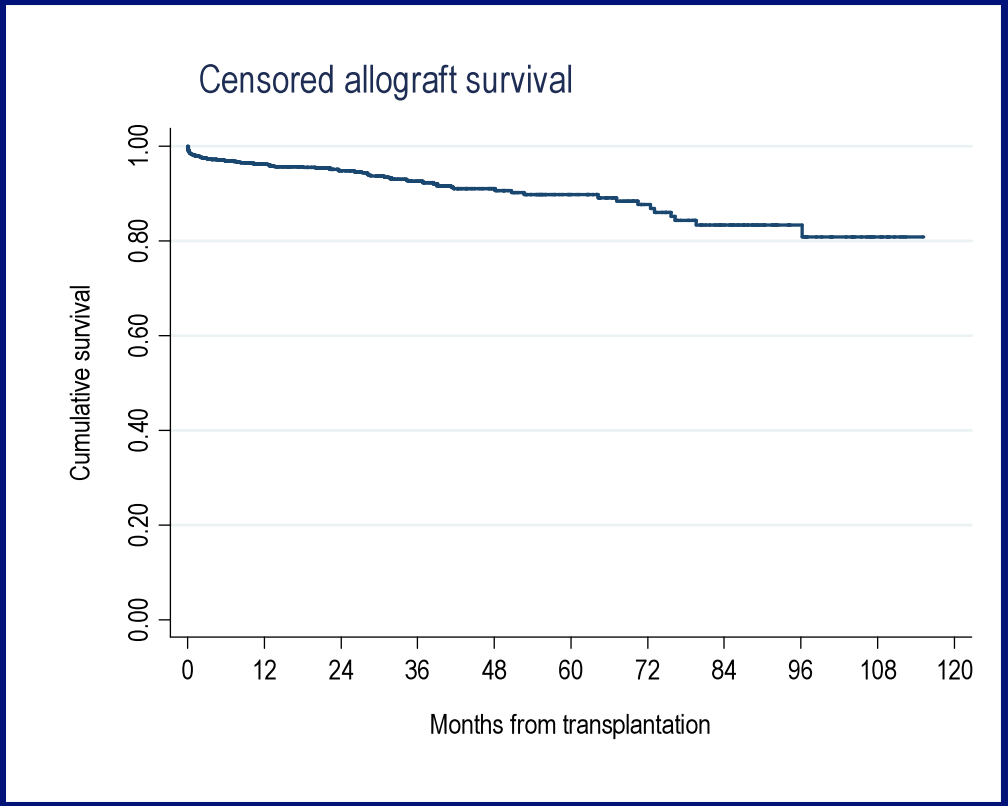
Allograft survival [censored for death with function]



Month	Cumulative survival	[95% ci]
12	96.3%	[94.5%,97.4%]
36	92.6%	[90.2%,94.4%]
60	89.8%	[86.6%,92.3%]
120	80.9%	[73.0%,86.8%]

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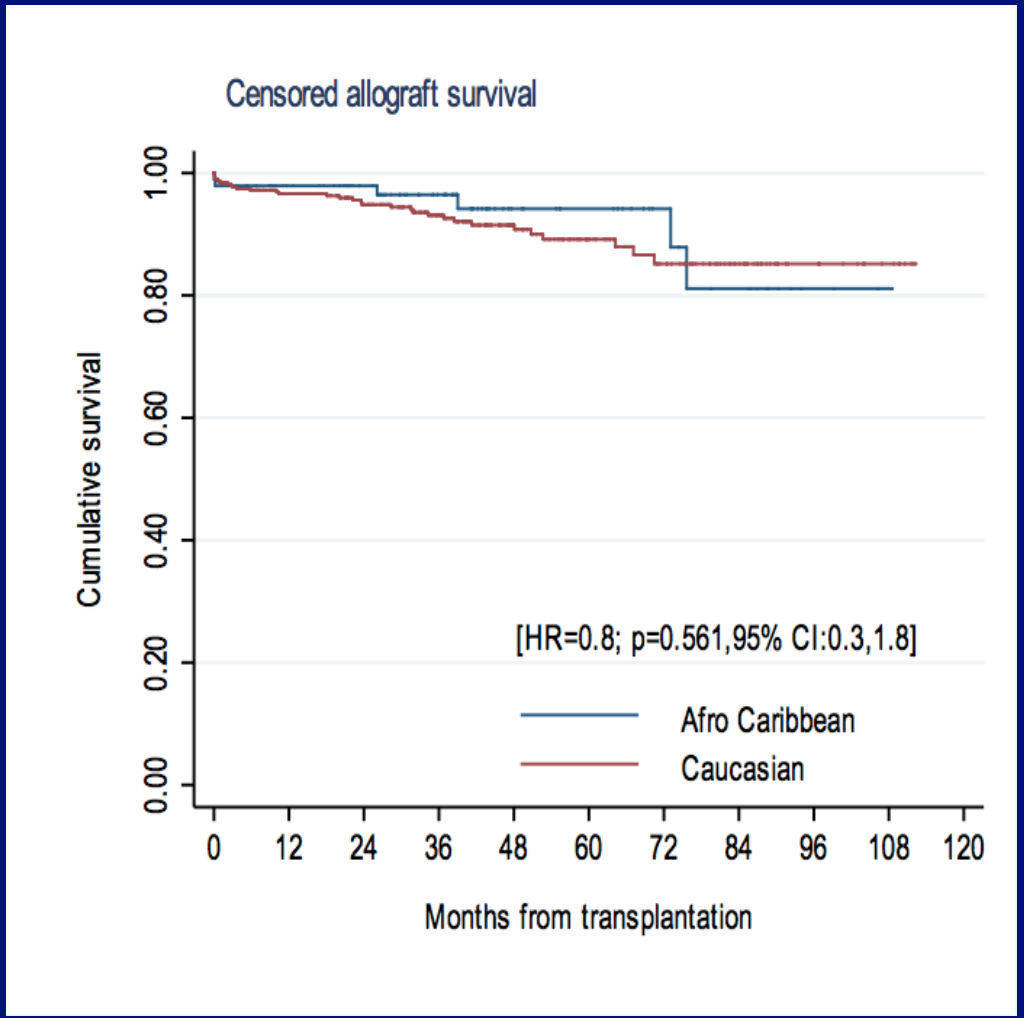
Censored allograft survival



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Allograft survival

10 year allograft survival [censored for death with function] is 81%

Causes of graft loss	
Rejection with compliance	13 [18.8%]
Rejection without compliance	10 [14.5%]
Technical failure	8 [11.6%]
Transplant glomerulopathy	7 [10.1%]
Withdrawal IS [overwhelming sepsis]	4 [5.8%]
Recurrent primary disease	3 [4.3%]
CNI toxicity	1 [1.4%]
Others	23 [33.3%]

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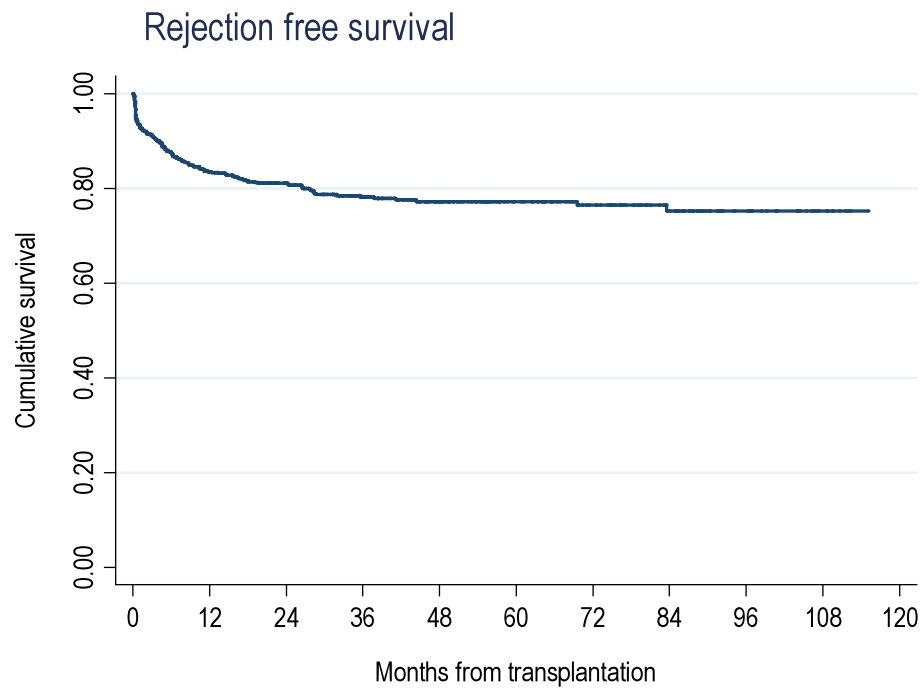
Rejection free survival



Month	Cumulative survival	[95% ci]
12	83.4%	[80.6%,85.9%]
36	78.2%	[74.8%,81.1%]
60	77.2%	[73.7%,80.3%]
120	75.2%	[70.6%,79.2%]

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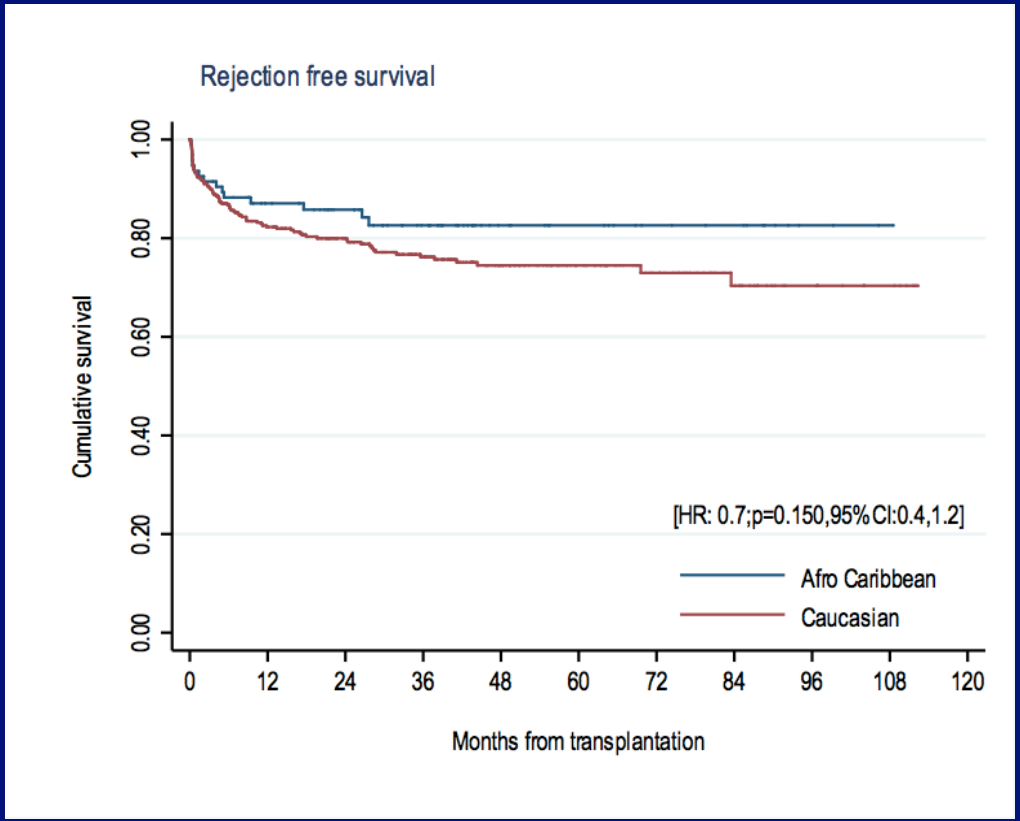
Rejection free survival



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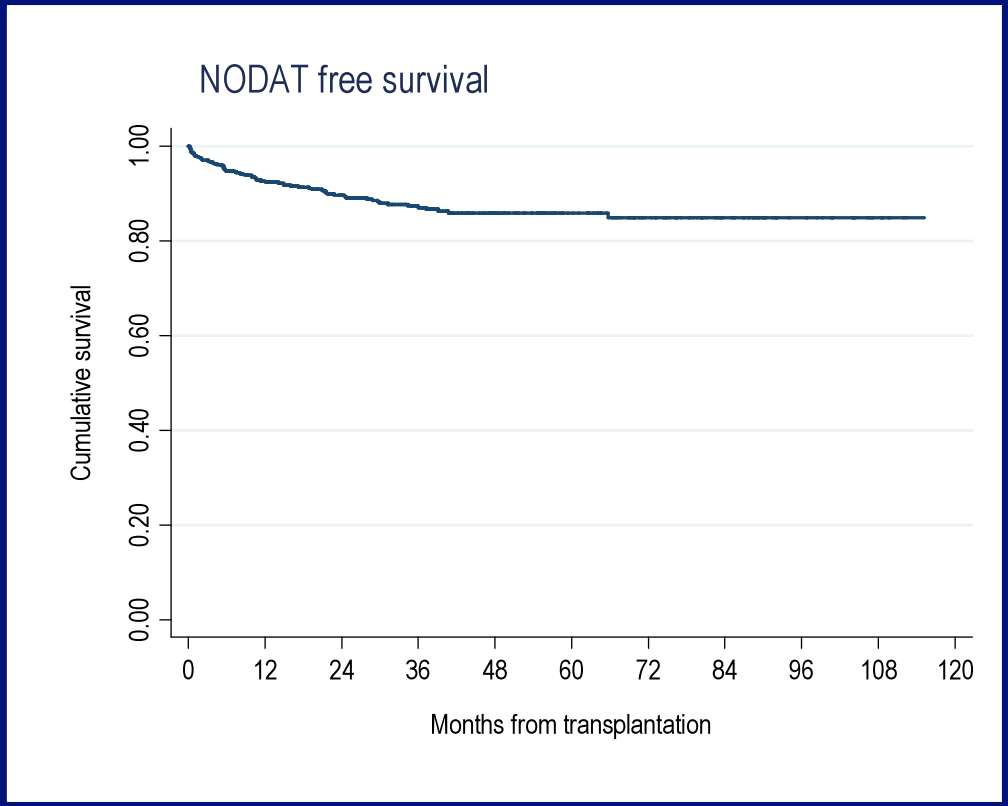
NODAT



Month	Cumulative survival	[95% ci]
12	92.6%	[90.1%,94.4%]
36	87.0%	[83.6%,89.7%]
60	85.8%	[82.1%,88.8%]
120	84.9%	[80.7%,88.2%]

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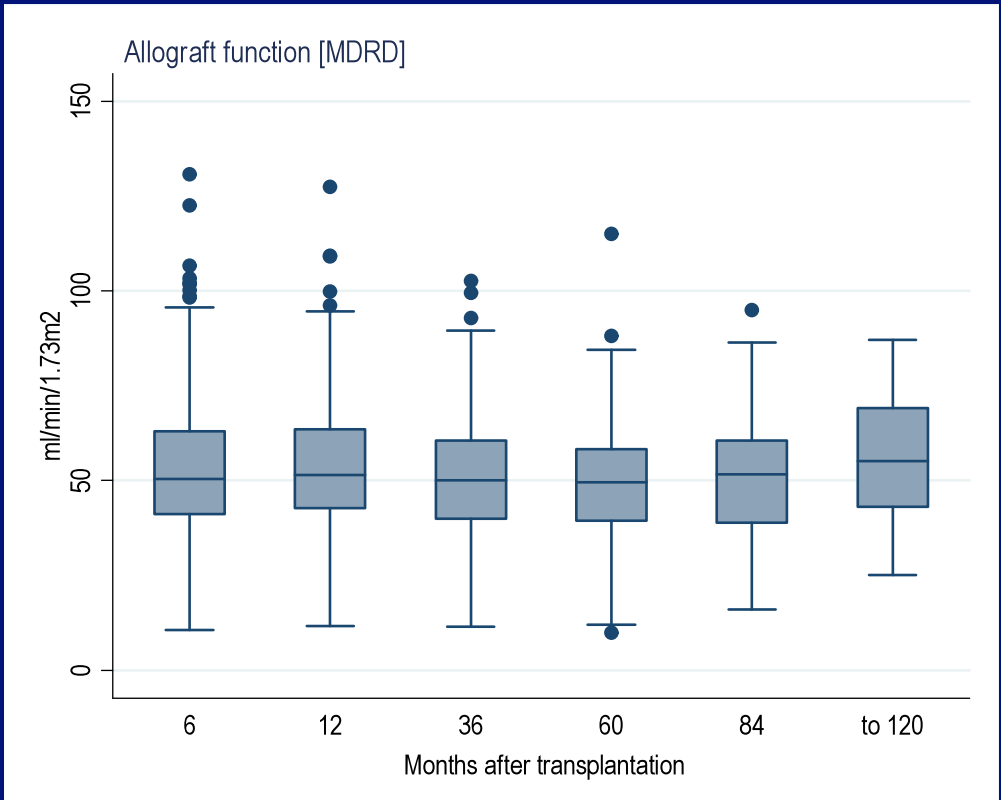
Allograft function



Changes in MDRD eGFR
-0.024 ml/min/1.73m^2 per year (95%ci -0.38,0.33)
p=0.893

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American Journal of Transplantation 2004; 4: 1845–1851
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2004.00583.x

Steroid Sparing with Tacrolimus and Mycophenolate Mofetil in Renal Transplantation

Richard Borrows*, Marina Loucaidou, Jen Van Tromp, Tom Cairns, Megan Griffith, Nadey Hakim, Adam McLean, Andrew Palmer, Vassilios Papalois and David Taube

Renal and Transplant Units, St. Mary's Hospital, Paddington, London, W2 1NY, UK
**Corresponding author: Richard Borrows, richardborrows@doctors.org.uk*

Conclusion:

Excellent long term graft and patient survival

Low incidence of late rejection

No increased risk of rejection or graft loss in Afro caribs

Low incidence of NODAT

Stable long term allograft function

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ABO Incompatible Living Renal Transplantation With a Steroid Sparing Protocol

Jack Galliford,[1,6] Rawya Charif,[1] Ka Kit Chan,[1] Marina Loucaidou,[1] Tom Cairns,[1] H. Terence Cook,[1,2] Anthony Dorling,[1,3] Nadey Hakim,[1] Adam McLean,[1] Vassilios Papalois,[1] Ranjan Malde,[4] Fiona Regan,[4,5] Martin Redman,[4] Anthony N. Warrens,[1,3] and David Taube[1]

(*Transplantation* 2008;86: 901–906)

10 patients

Tacrolimus/ MMF/ steroid sparing

Rituximab and Daclizumab

Centrifuge plasma exchange/ ivIg pre and post op.

Campath

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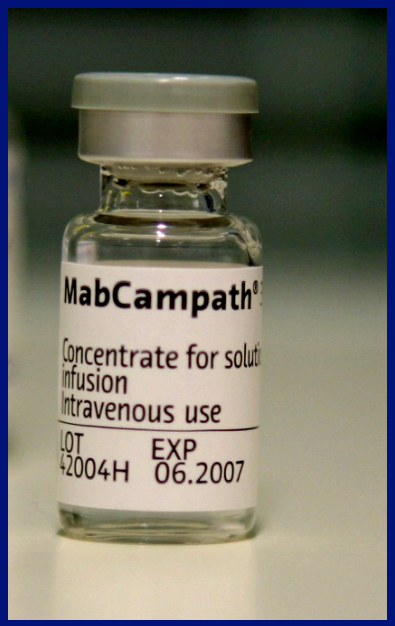
Campath induction in renal transplantation



Campath widely used as an induction agent in renal transplantation
Many historical studies with a variety of immunosuppressive agents
- Ciclosporin
- Sirolimus
- Tacrolimus
- Generally report good short term outcomes [1 – 3 years]

Only one longer term study [5 years]

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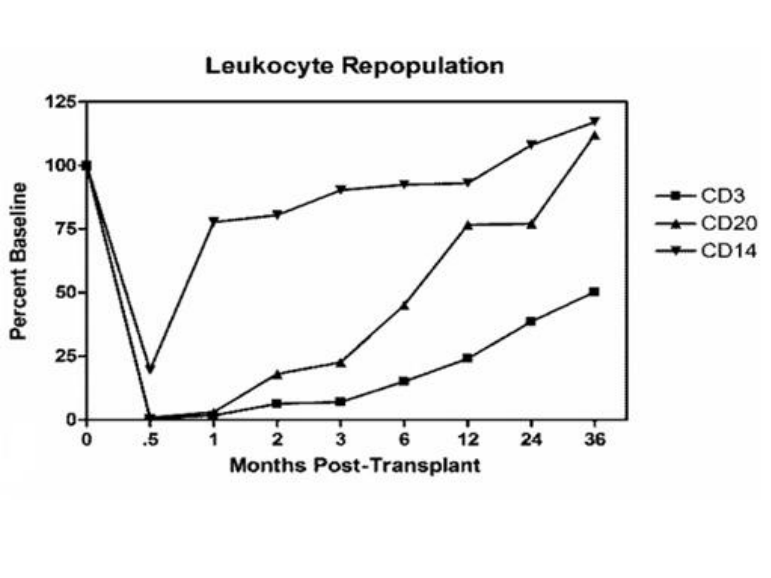
Campath 1-H [Alemtuzumab]



CD52 antigen expressed on T cells, B cells and monocytes

Highly effective depleting antibody

Associated with low rates of rejection

Allows reduction in maintenance immunosuppression

Bloom et al, Transplantation 2006

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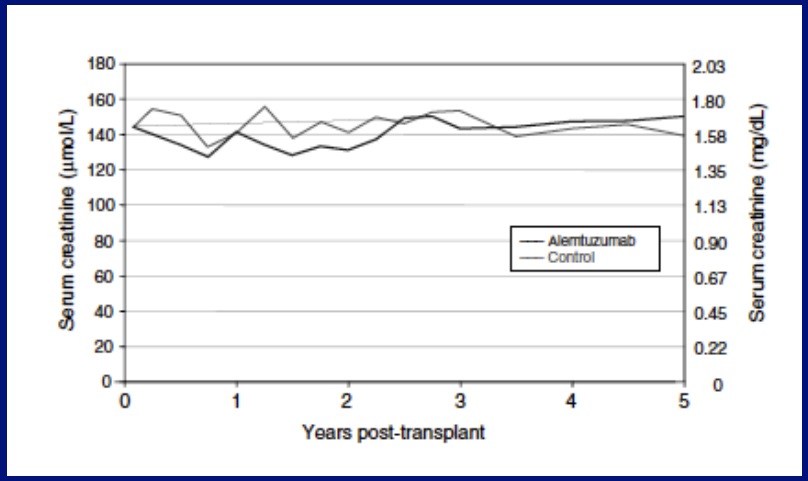
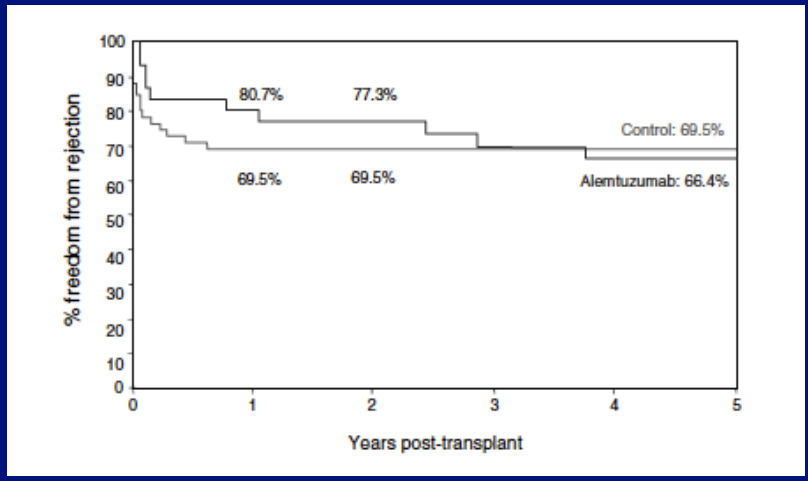
American Journal of Transplantation 2005; 5: 1347–1353
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2005.00822.x

Alemtuzumab (CAMPATH 1H) Induction Therapy in Cadaveric Kidney Transplantation—Efficacy and Safety at Five Years





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American Journal of Transplantation 2005; 5: 1347–1353

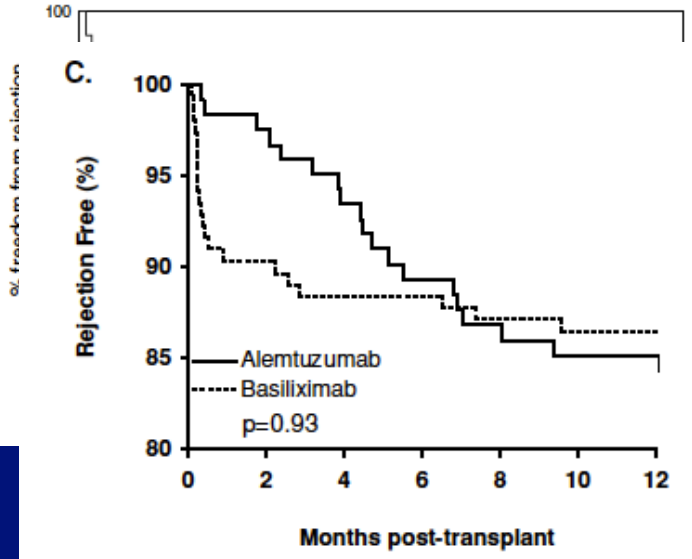
American Journal of Transplantation 2005; 5: 2539–2548
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2005.01067.x

Alemtuzumab Induction and Prednisone-Free Maintenance Immunotherapy in Kidney Transplantation: Comparison with Basiliximab Induction—Long-Term Results

Table 6: Serum creatinine values in kidney transplant recipients receiving prednisone-free maintenance immunosuppression and either alemtuzumab or basiliximab induction

Time post-transplant (month)	Alemtuzumab	Basiliximab	p-Value
0	8.14 ± 3.20	9.01 ± 3.72	
1	1.51 ± 0.75	1.54 ± 0.49	ns
6	1.38 ± 0.56	1.39 ± 0.55	ns
12	1.42 ± 0.59	1.36 ± 0.48	ns
24	1.41 ± 0.52	1.45 ± 0.68	ns
36	1.52 ± 0.72	1.42 ± 0.65	ns



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American Journal of Transplantation 2005; 5: 1347–1353

American Journal of Transplantation 2005; 5: 2539–2548
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2005.01067.x

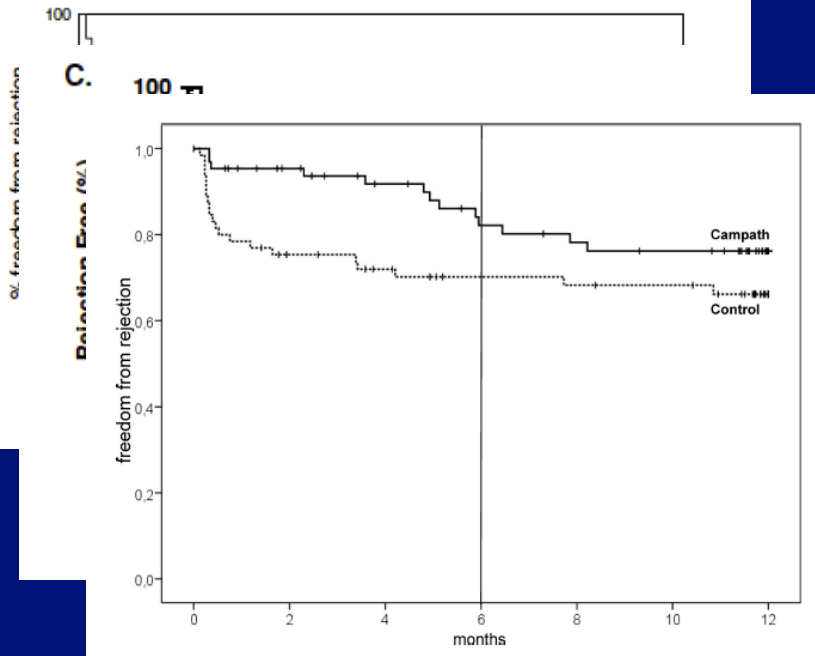
American Journal of Transplantation 2008; 8: 1480–1485
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2008.02273.x

Alemtuzumab (Campath-1H) and Tacrolimus Monotherapy After Renal Transplantation: Results of a Prospective Randomized Trial

Table 5: Adverse events

	Campath group n = 65	Control group n = 66	
Infections			
Viral: non-CMV	16	15	RR = 1.08 (0.59–2.00)
CMV	18	8	RR = 2.28 (1.07–4.88)
Bacterial	17	29	RR = 0.60 (0.36–0.97)
Fungal	7	9	RR = 0.79 (0.31–1.99)
Cardiovascular	13	14	RR = 0.94 (0.48–1.85)
Gastrointestinal	30	30	RR = 1.02 (0.70–1.47)
Hematologic	49	48	RR = 1.04 (0.85–1.27)
Metabolic			
Hyperlipidemia	19	18	RR = 1.07 (0.62–1.85)
New onset diabetes	2	2	RR = 1.02 (0.15–6.99)
Malignancies	0	0	



Campath at Imperial College

In 2004, we set out to develop a simple immunosuppressive regime to

1. Reduce Tacrolimus nephrotoxicity [use lower Tac levels]
2. Reduce costs
3. Steroid sparing
4. Comply with NICE guidelines [no MMF]

In November 2005, we started a formal RCT.
Recruitment finished in April 2008.

3 year results.

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West London CamTac RCT

Study arm:

Campath induction, 30 mgs iv peri operatively

Tacrolimus monotherapy [0.1 mgs/kg/day]

Levels by LCMS 5 – 8 ng/ml

Steroid sparing

No MMF

Control arm:

Daclizumab induction, 2.0 mgs/kg day 0 and day 14

Tacrolimus 0.15 mg/kg/day

Levels by LCMS 8 -11 ng/ml for the first 12 months, subsequently 5 – 8 ng/ml

Steroid sparing

MMF 750 mgs bd to achieve MPA levels 2 -3 mg/l

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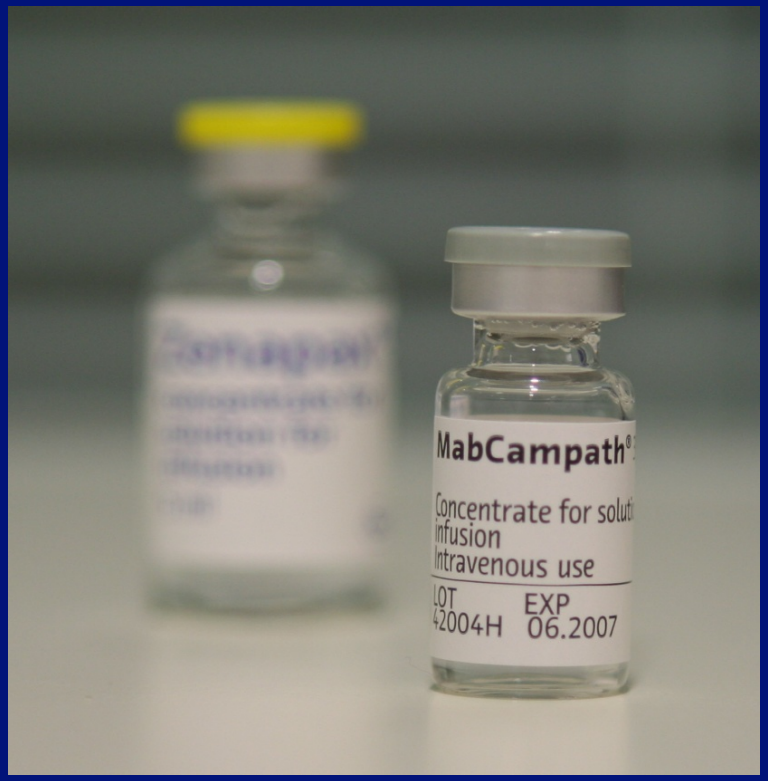
West London CamTac RCT



Exclusions

1] Patients who had received significant amounts of myelosuppressive agents

2] Patients transplanted with grafts from NHB donors

3] Patients who are hepatitis B or C+ or HIV +

4] SPK transplants

5] ABOi or FXM + transplants

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West London CamTac RCT

Primary Outcomes

Patient survival with functioning graft at 1 year. [10% non inferiority margin]

Secondary Outcomes:

1] Allograft function

2] Occurrence and nature of rejection

3] Development of Donor specific antibodies [DSAbs]

4] Surveillance biopsies 6 – 12 months

5] Adverse events [infection, PTLD, AI disease]

6] Drug costs

Ethics

COREC approval

Local ICKTI approval

Trial was registered at clinical trials. gov, identifier NCT00246129

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West London CamTac RCT design

1] Stratified for live and deceased donors

2] Randomization: 2:1 Campath and Daclizumab - MMF arms

3] Powered to detect a 10% non inferiority in patient survival with functioning graft during the first year

4] Target enrolment: 80 patients in the Campath arm and 40 in the Daclizumab – MMF arm

Recruitment completed on 2nd April 2008

Donor type	**Campath** n=82	**Daclizumab - MMF** n=41
Deceased donor	30 [36.6%]	16 [39.0%]
Live donor	52 [63.4%]	25 [61.0%]

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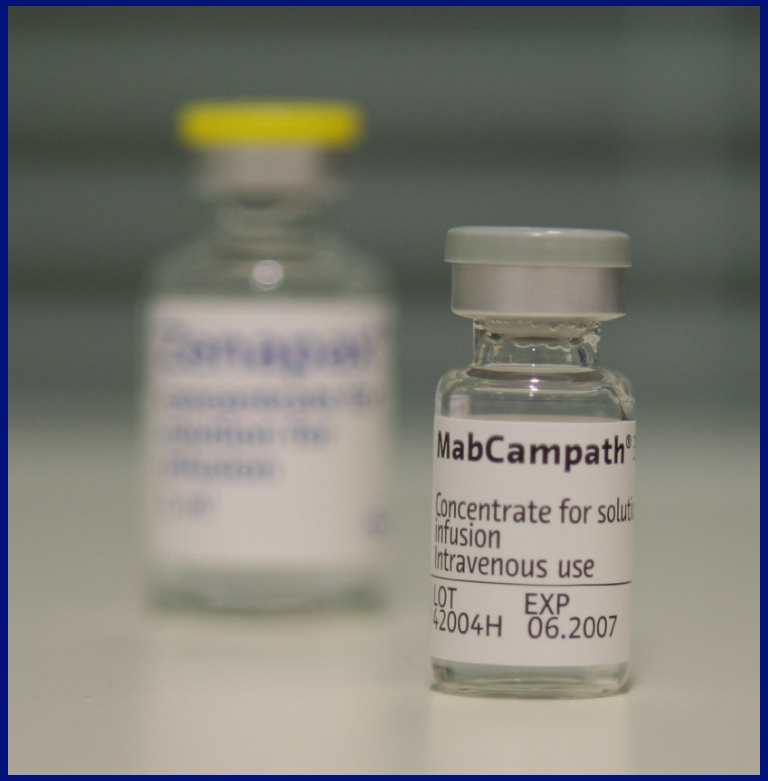
West London CamTac RCT



Rejection

Rejection was diagnosed by biopsy

Rejection was treated with iv methyl prednisolone, oral prednisolone for 3 months and the addition of MMF.

Prophylaxis

CMV : Valganciclovir for 3 months

PCP: Septrin for 6 months

Statistics

Student t, Fisher Exact, Log rank and Wilcoxon tests

Rate ratio estimated using generalised linear model [Poisson]

Stata 11.1 [StataCorp, Texas]

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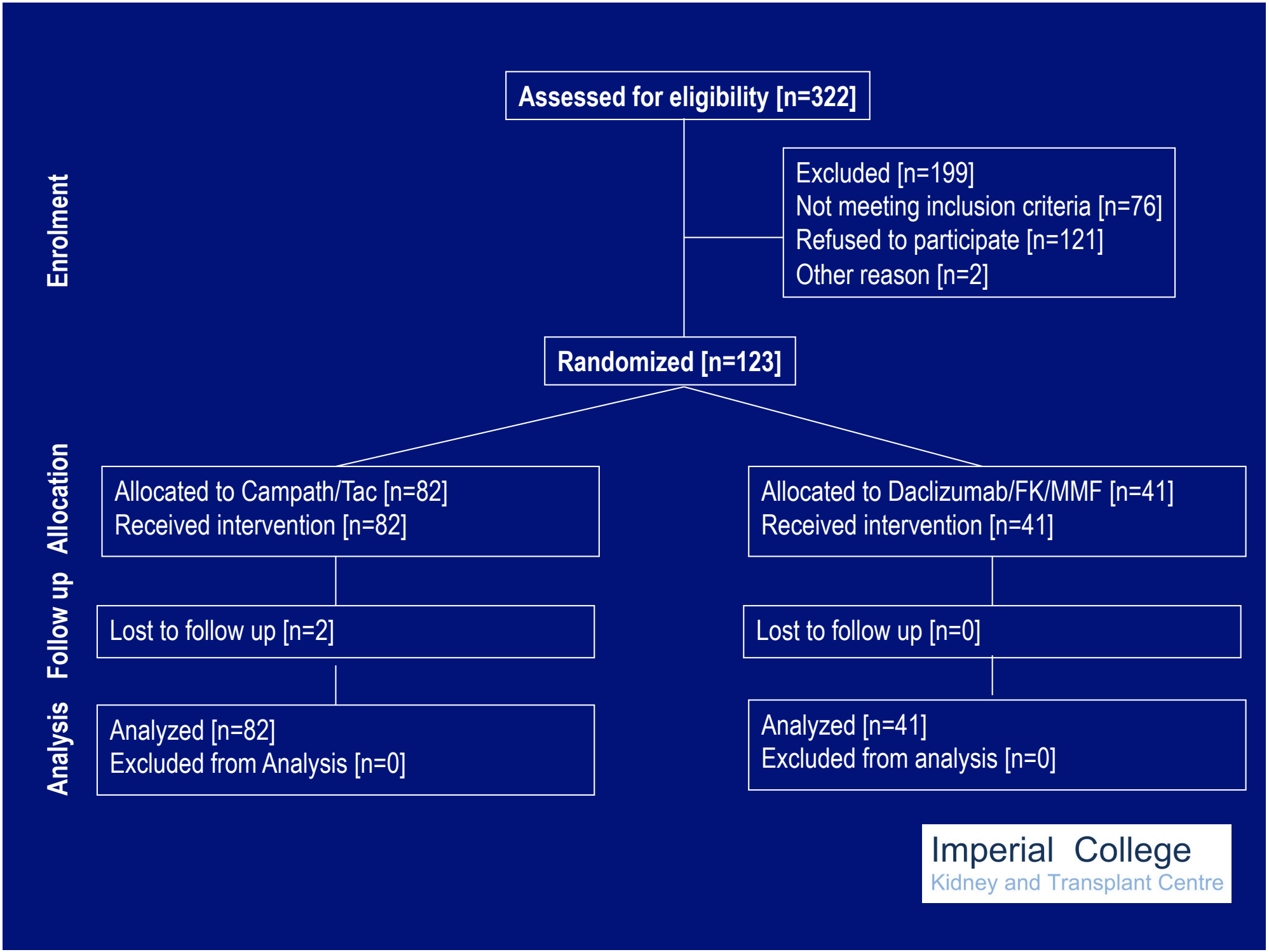
Enrolment
Assessed for eligibility [n=322]
Excluded [n=199]
Not meeting inclusion criteria [n=76]
Refused to participate [n=121]
Other reason [n=2]
Randomized [n=123]
Allocation
Allocated to Campath/Tac [n=82]
Received intervention [n=82]
Allocated to Daclizumab/FK/MMF [n=41]
Received intervention [n=41]
Follow up
Lost to follow up [n=2]
Lost to follow up [n=0]
Analysis
Analyzed [n=82]
Excluded from Analysis [n=0]
Analyzed [n=41]
Excluded from analysis [n=0]
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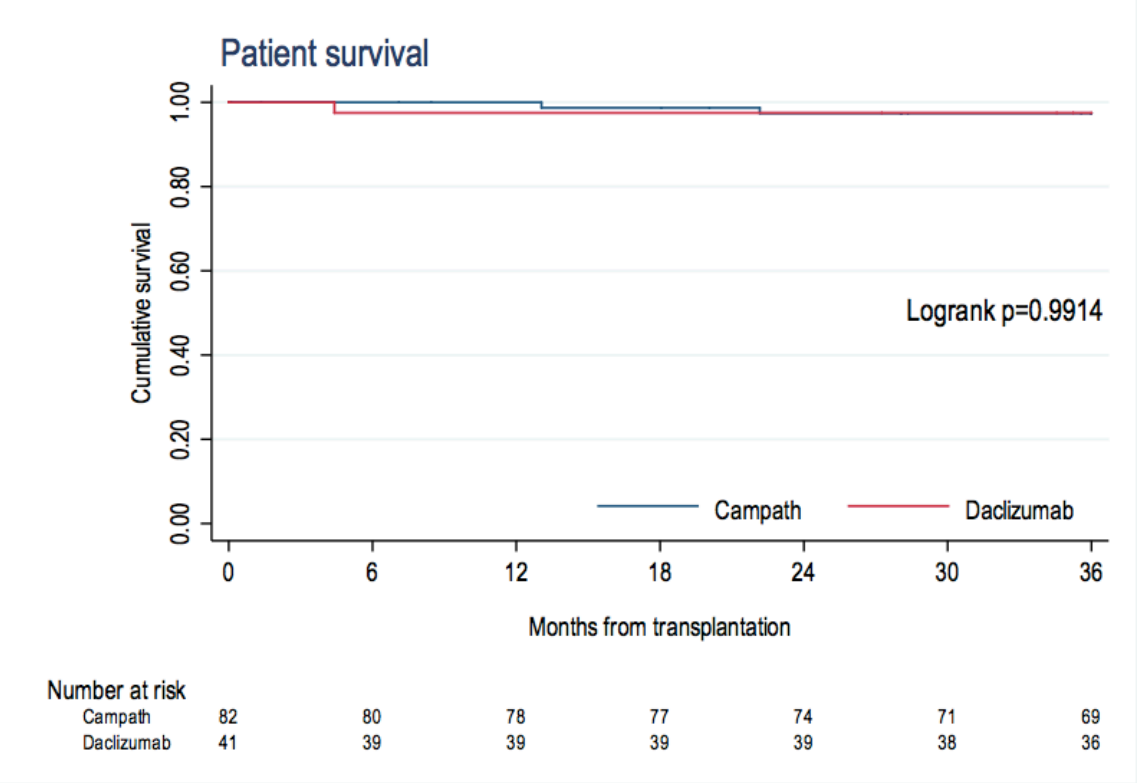
Patient Survival



	Campath	Daclizumab
1	100.0%	100.0%
3	100.0%	100.0%
6	100.0%	97.5%
12	100.0%	97.5%
24	97.4%	97.5%
36	97.4%	97.5%

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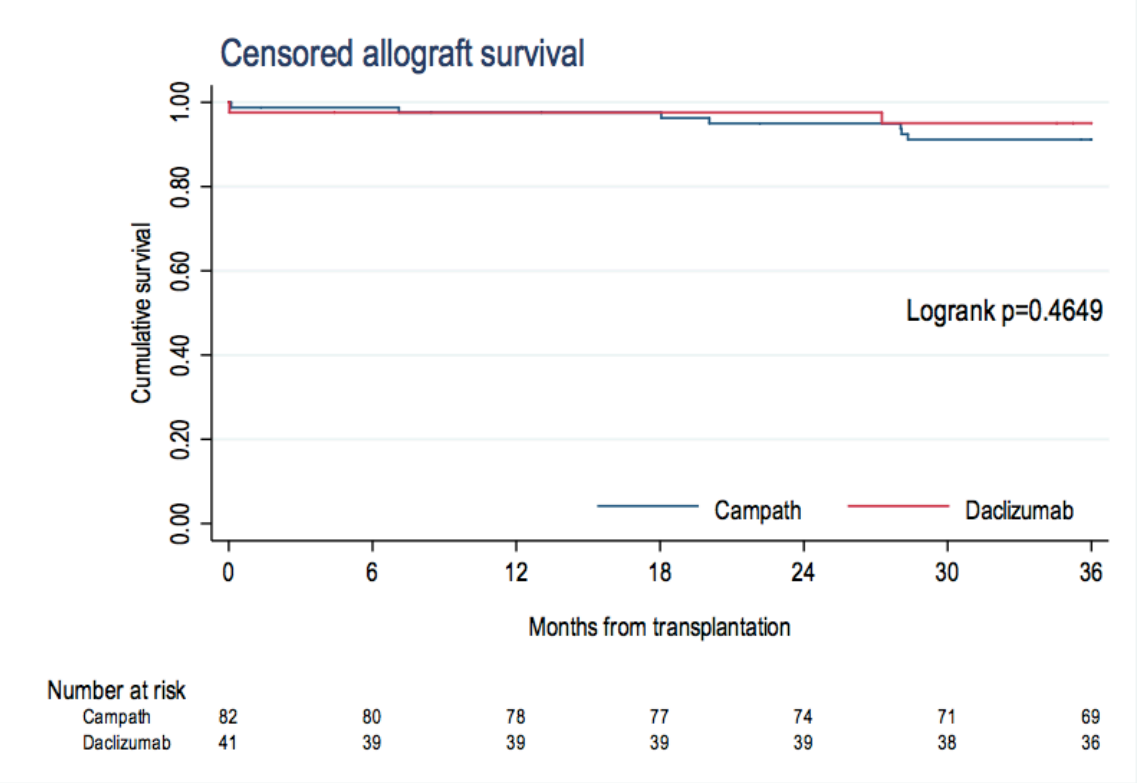
Allograft survival [censored for death with function]



	Campath	Daclizumab
1	98.8%	97.6%
3	98.8%	97.6%
6	98.8%	97.6%
12	97.6%	97.6%
24	95.0%	97.6%
36	91.2%	95.1%

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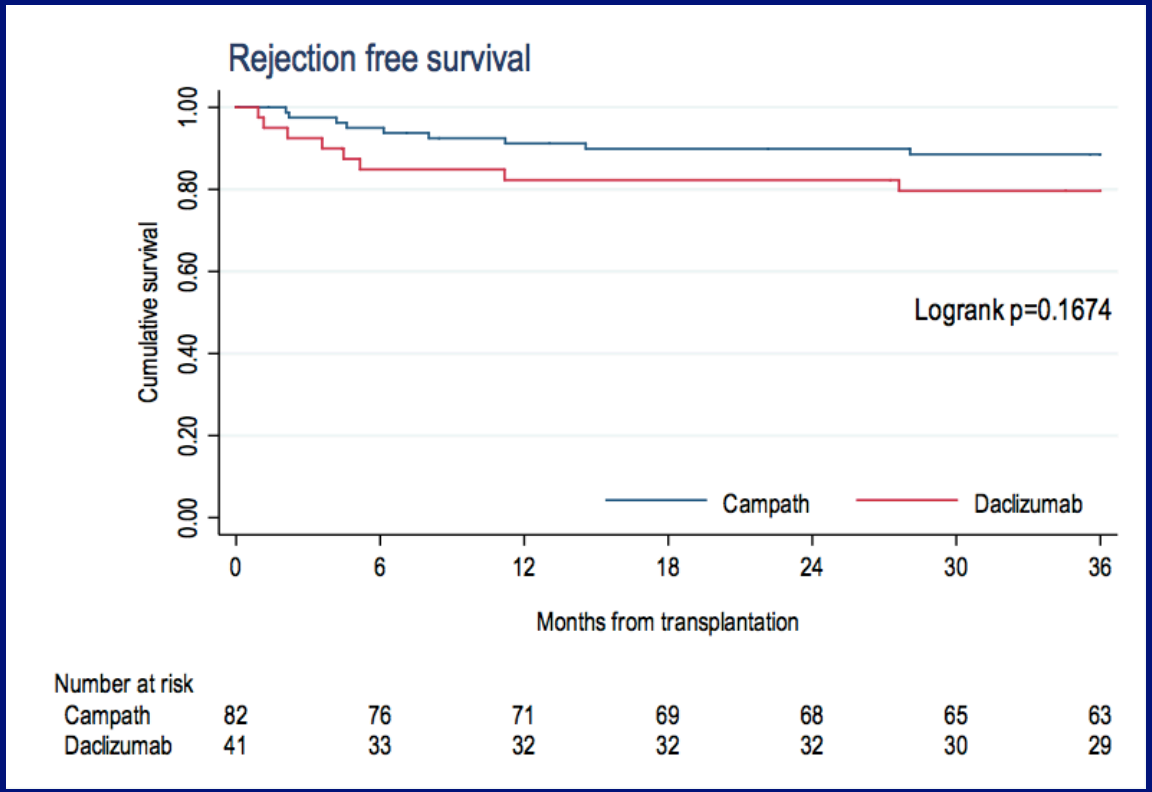
Rejection free survival



	Campath	Daclizumab
1	100.0%	97.5%
3	97.5%	92.5%
6	95.0%	84.9%
12	91.2%	82.3%
24	89.9%	82.3%
36	88.6%	79.6%

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Type of rejection

Banff Class	Campath	Daclizumab	p
Ia	7 [8.5%]	8 [19.5%]	0.08
Ib	2 [2.4%]	1 [2.4%]	0.99
IIb	3 [3.7%]	1 [2.4%]	0.59
aAMR	1 [1.2%]	1 [2.4%]	0.99

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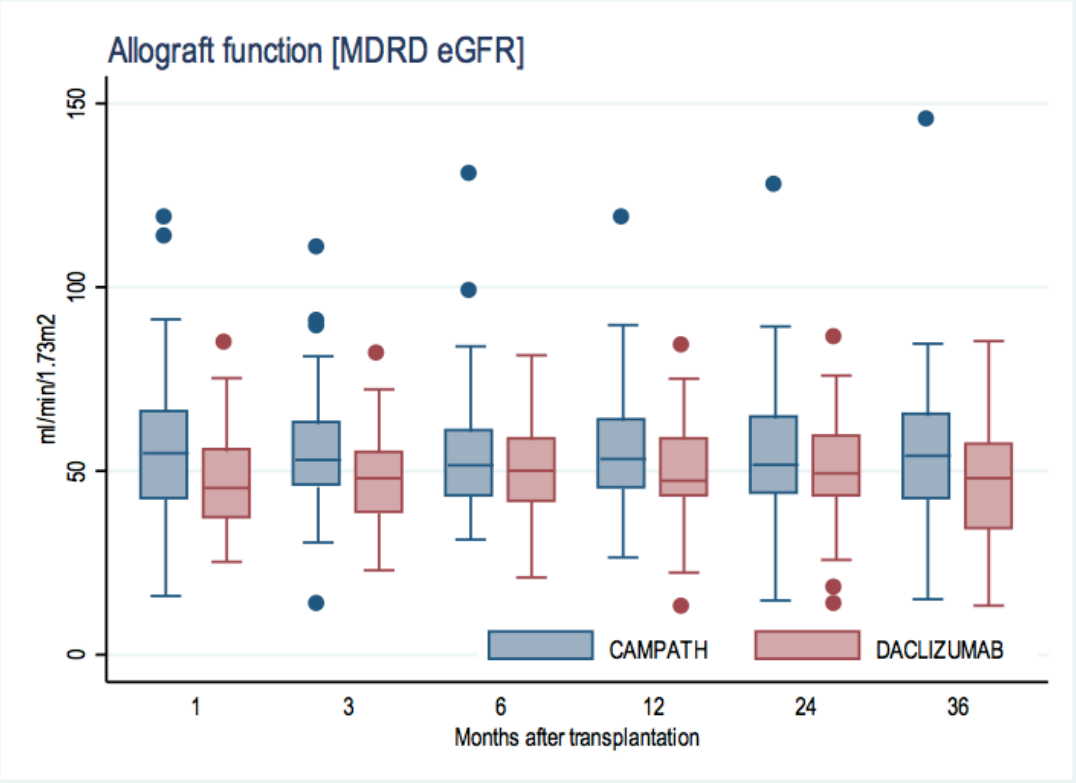
Allograft function



	Campath	Daclizumab	p
1	55.9 ± 4.2	45.9 ± 5.3	0.006
3	54.8 ± 3.2	45.8 ± 4.9	0.003
6	52.9 ± 3.6	48.5 ± 4.7	0.166
12	55.4 ± 3.6	49.4 ± 4.8	0.060
24	54.6 ± 3.8	49.4 ± 4.9	0.116
36	54.8 ± 4.9	47.5 ± 6.7	0.113

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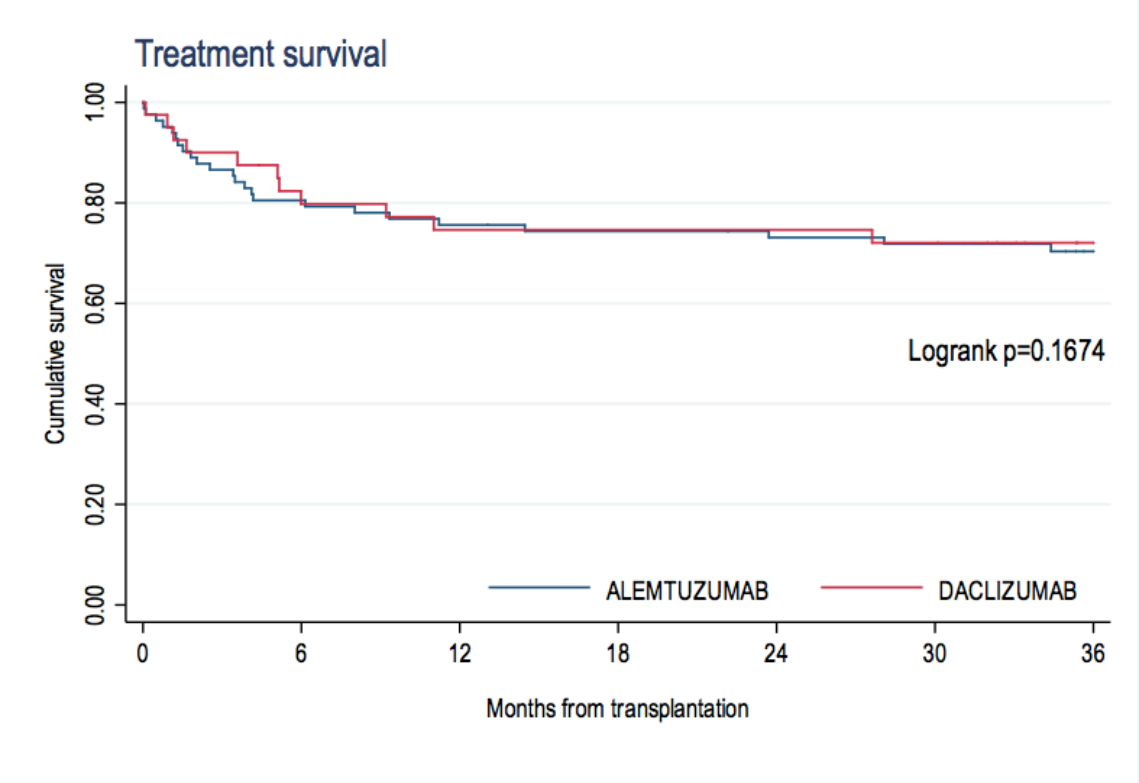
Treatment survival



	Campath	Daclizumab
1	95.1%	95.0%
3	86.6%	90.0%
6	80.5%	79.8%
12	75.6%	74.6%
24	73.1%	74.6%
36	70.4%	72.1%

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Adverse events

	Campath	Daclizumab	Relative risk [95% CI]	p value
Infections*				
UTI	31 [38·6]	9 [22·9]	1·6 [0·49-5·81]	0·406
Bacteraemia	15 [18·6]	9 [22·9]	0·82 [0·24-2·73]	0·743
Wound infection	6 [7·6]	6 [15·4]	0·5 [0·16-1·51]	0·213
CMV Disease	1 [1·2]	4 [10·2]	0·12 [0·01-1·08]	0·058
Others	6 [7·6]	2 [5·1]	1·47 [0·63-7]	0·628
Total infections	59 [73·2]	30 [76·3]	1·0 [0·62-1·47]	0·839
Other adverse events:				
PTLD	0	0		
ITP	1	0		
Other auto-immune disease	0	0		
New onset diabetes	4	5		0·229

*Episodes [Incidence per 100 patient-years]

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Drug costs [mean per patient, per year, using BNF prices]

		1st year	Subsequent years
Campath	Induction	£275	£0
	Tacrolimus	£3,082	£3,200
	MMF	£130	£25.16
	Total	£3,488.00	£3,225
Daclizumab	Induction	£2,505	£0
	Tacrolimus	£3,723	£3,110
	MMF	£1,293	£1,342
	Total	£7,521.00	£4,452
	Saving per patient	**£4,033.00**	**£1,226.84**
	Saving per 100 patients	**£ 400k**	**£120k**

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Summary of CamTac

1] 3 year patient and allograft survival are similar in both groups.

2] Trend to better allograft function in Campath group

3] Incidence and nature of rejection are similar in both groups

4] No increased late rejection in the Campath group

5] Campath regime is significantly cheaper

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What's going on elsewhere?

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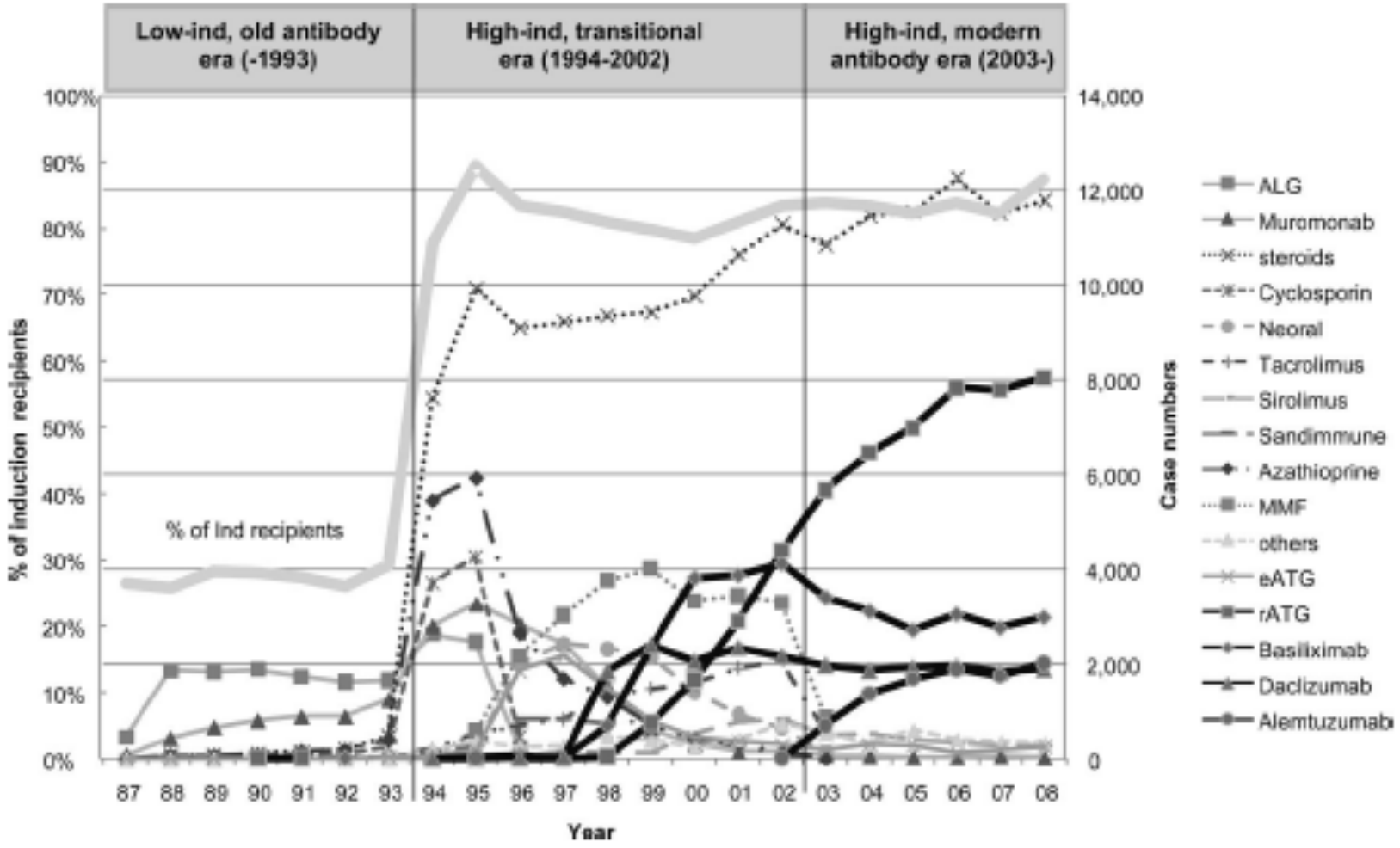
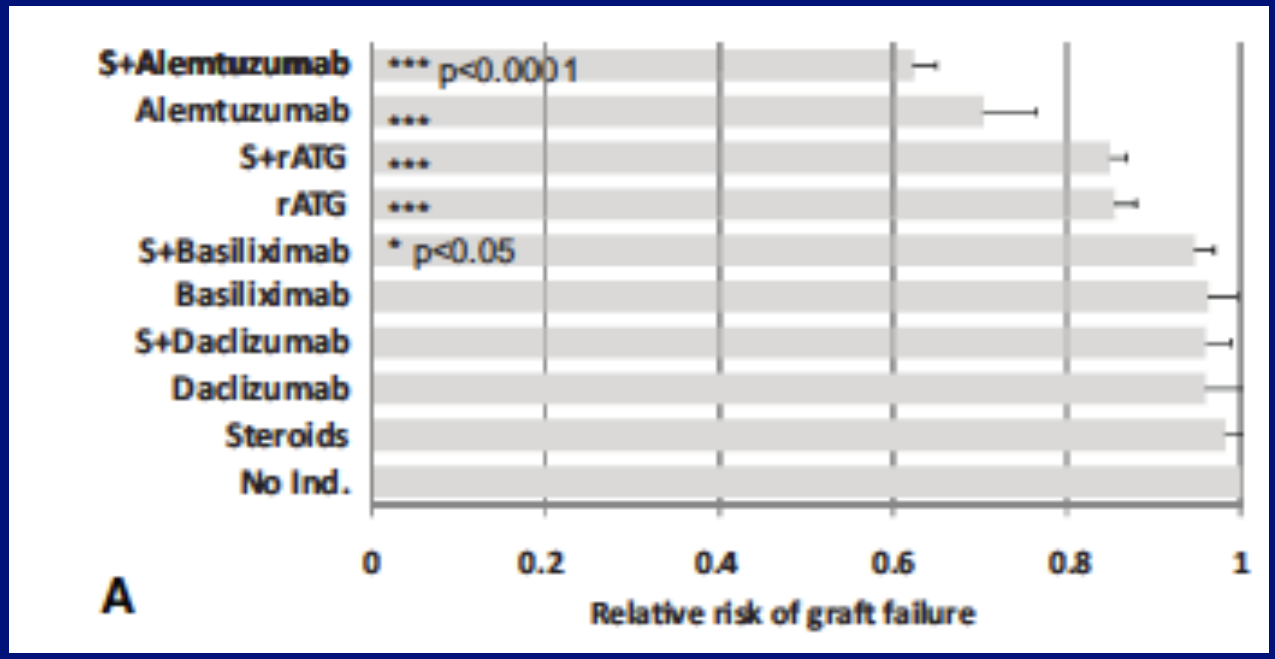
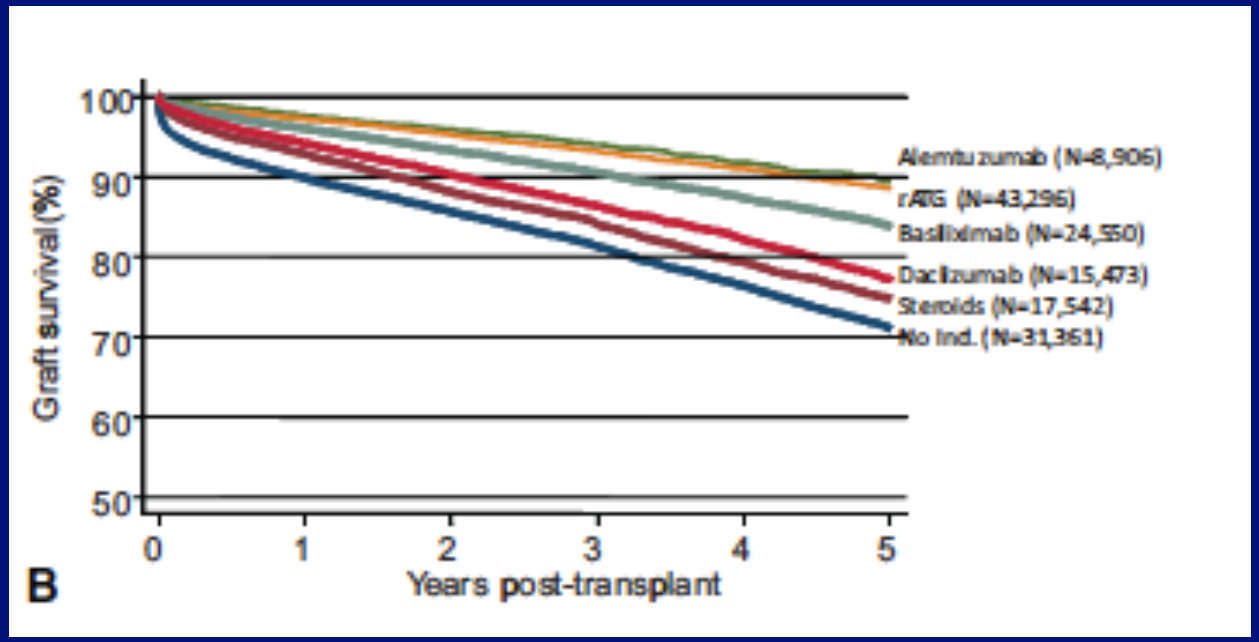
Induction Immunosuppression Improves Long-Term Graft and Patient Outcome in Organ Transplantation: An Analysis of United Network for Organ Sharing Registry Data

Junchao Cai and Paul I. Terasaki







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Question] Minimisation of immunosuppression: Necessary or Necessity?

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Answer] Minimisation of immunosuppression: Necessary AND Necessity?

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