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Alemtuzumab-based induction treatment versus basiliximab based induction treatment in kidney transplantation (the 3C Study): a randomised trial

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Background and Rationale

- Despite substantial improvements in acute rejection, the long-term rate of transplant failure has not improved over the past two decades.
- ?CNI contribution in delayed graft failure

- If increase potency of induction agents using Campath, can we reduce CNI exposure?
- *Does delayed conversion (6 months) to sirolimus allow complete withdrawal of CNIs?*

Induction Treatment options and guidelines

Monoclonal (Basiliximab, alemtuzemab, OKT3)

Polyclonal (ATG)

T-cell depleting (ATG, alemtuzemab, OKT3)

Non depleting (basiliximab)

1.2: We recommend including induction therapy with a biologic agent as part of the initial immunosuppressive regimen in KTRs. *(1A)*

1.2.1: We recommend that an IL2-RA be the first-line induction therapy. *(1B)*

1.2.2: We suggest using a lymphocyte-depleting agent, rather than an IL2-RA, for KTRs at high immunologic risk. *(2B)*

- The number of human leukocyte antigen (HLA) mismatches (A)
- Younger recipient age (B)
- Older donor age (B)
- African-American ethnicity (in the United States)
- PRA >0% (B)
- Presence of a donor-specific antibody (B)
- Blood group incompatibility (B)
- Delayed onset of graft function (B)
- Cold ischemia time >24 hours (C)

	Type	Action	Pros	Cons
Basiliximab (Simulect)	Monoclonal Non-depleting	Anti-CD25 IL2R blocker CD25 only expressed on activated T cells	• No side effects! • No drug interactions • No ↑ malignancy or infection	• Not as effective in sensitised patients (memory T cells can still proliferate)
ATG	Polyclonal Depleting	Anti-CD3,CD4,CD8 , CD25++ Blocks all 3 signals in T cell activation	• ↓AR> IL2R Ab • Also suppresses B cells/plasma cells	• Anaphylaxis • Cytokine release • ↓WCC and Plt • Infections • PTLD • Serum sickness • Needs CVC
OKT3	Monoclonal Depleting	Anti-CD3 All T cells >90% clearance of CD3 cells within 24hrs	• Tends not to cause ↓plts or ↓WCC	• Horrific S/E! (anaphylaxis, cytokine release syndrome, infections, PTLD) • Short-lasting, rebound CD3
Alemtuzemab (Campath)	Monoclonal Depleting	Anti-CD52 (T and B cells) Not activate cells, but targets them for comp-mediated lysis/opsonisation	• Potential to minimise IS- "prope tolerance"	• Pancytopenia (↓L ø count persists for 6/12) • Some cytokine release • PTLD, CMV • ↑AI disease (TFT, ITP, HA) • ? ↑ AMR
Rituximab	Monoclonal	Anti CD20 (B cells) Reduce APC presentation to T cell		• V limited experience and too few trials

Study groups and outcomes

CAMPATH induction

LOW DOSE tac and Myfortic with NO STEROIDS

BASILIXIMAB induction

STANDARD DOSE tac , Myfortic and steroids

Primary Outcome:

- Incidence of Bx proven AR in 1st 6/12

Secondary Outcomes:

- Graft related outcomes (graft survival, CAN)
- Safety outcomes (infection, malignancy, survival)
- Other events of interest (NODAT, anaemia, leucopenia, thrombocytopenia, HTN)

Methods

- 18 tx centres in UK (including UHW)

- Inclusion
  - 18yrs +
  - Scheduled to receive kidney Tx in next 24hrs
- Exclusion
  - Multi-organ tx
  - Previoius rx with Campath
  - Active infection
  - Malignancy in last 5 years

- Randomisation balanced for age, sex, ethnicity, type of Tx (DBD/DCD/LD), HLA mismatch, Highly sensitised, previous Tx

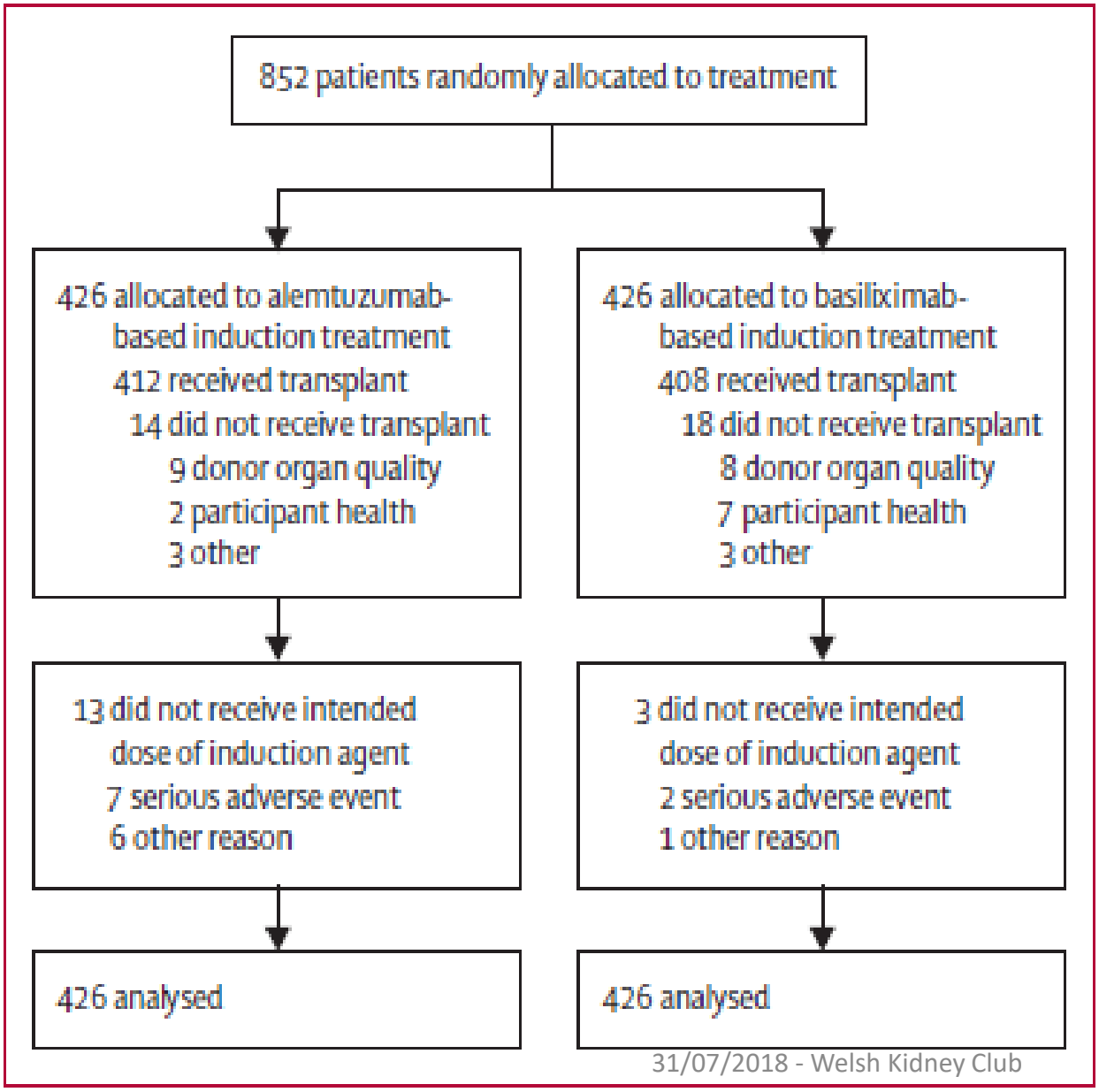
Methods continued

- Study Clinic visits at months 1,3,6,9,12
- Recorded BP, weight, bloods, tac level, uPCR
- Recorded any serious and non-serious AE
- All transplant rejection/failure episodes recorded
- All cancer diagnoses flagged to UK Transplant registry

Statistical Analyses

- 90% power to detect a 50% proportional reduction of rejection episode at $p<0.05$
- Safety and efficacy analysed using intention-to-treat comparisons
- Cox regression used for time-to-event analyses

Results



Study period:
Oct 4, 2010, and Jan 21, 2013

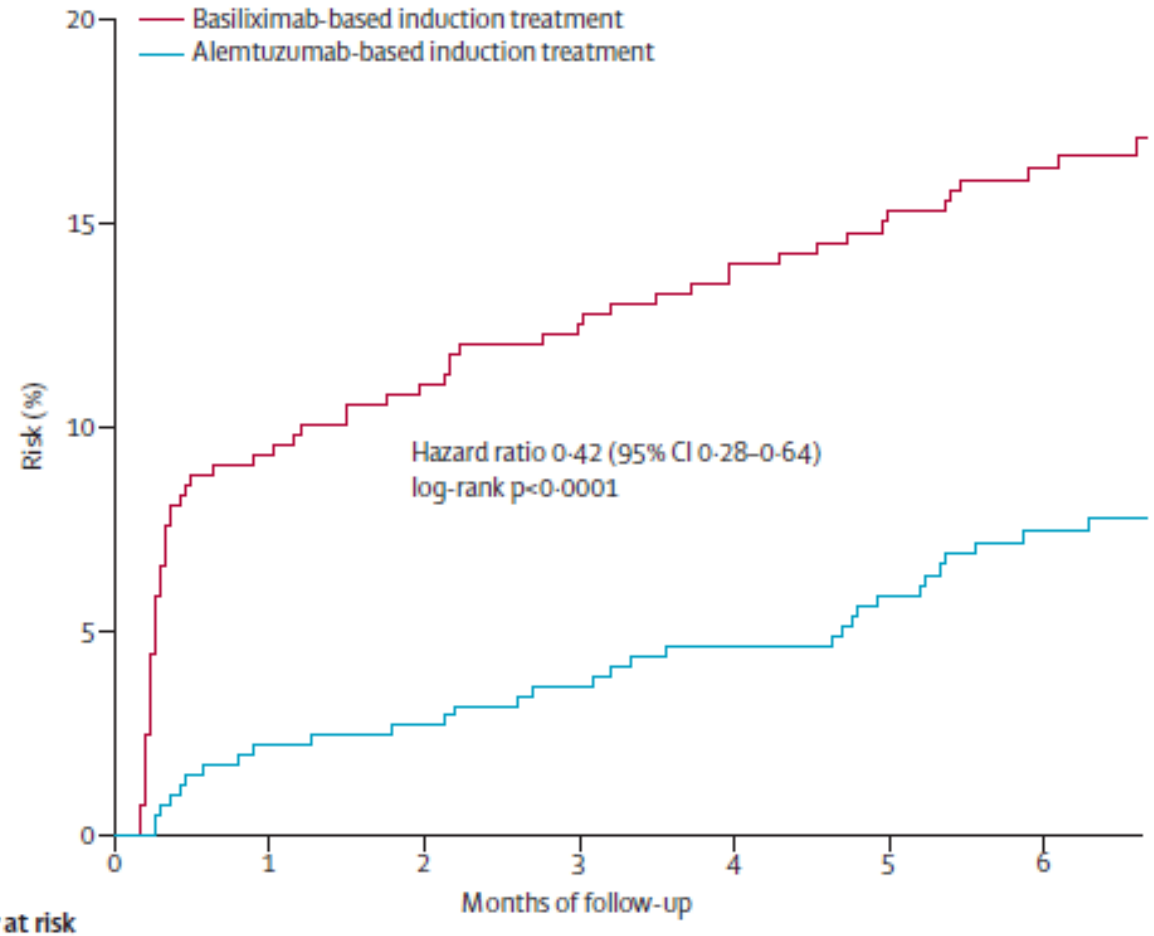
Max f/up: 12 months post Tx

Baseline Demographics

- Mean age recipient: 52years
- Predominantly white (87%) males (65%)
- HD at baseline was the only difference (57% in Campath gp cf 50% in simulect gp)

Virology serology		
CMV-positive donor to negative recipient	104 (24%)	102 (24%)
EBV-positive donor to negative recipient	21 (5%)	19 (4%)
Type of donor		
Donation after brain death	148 (35%)	145 (34%)
Donation after circulatory death	158 (37%)	158 (37%)
Donation from living (related or unrelated) patient	120 (28%)	123 (29%)
Mean donor age in years	50·2 (14·9)	51·6 (14·6)
Donor sex		
Male	215 (50%)	207 (49%)
Female	193 (45%)	179 (42%)
Unknown	18 (4%)	40 (9%)
Cold ischaemia time (h)‡	13·9 (5·7)	12·9 (6·0)

Primary Outcome-Rates of AR



Number at risk							
Basiliximab-based induction treatment	426	370	361	355	347	342	273
Alemtuzumab-based induction treatment	426	400	398	394	388	383	305

31(7%) BPAR in Campath group

Cf

68 (16%) BPAR in basiliximab group

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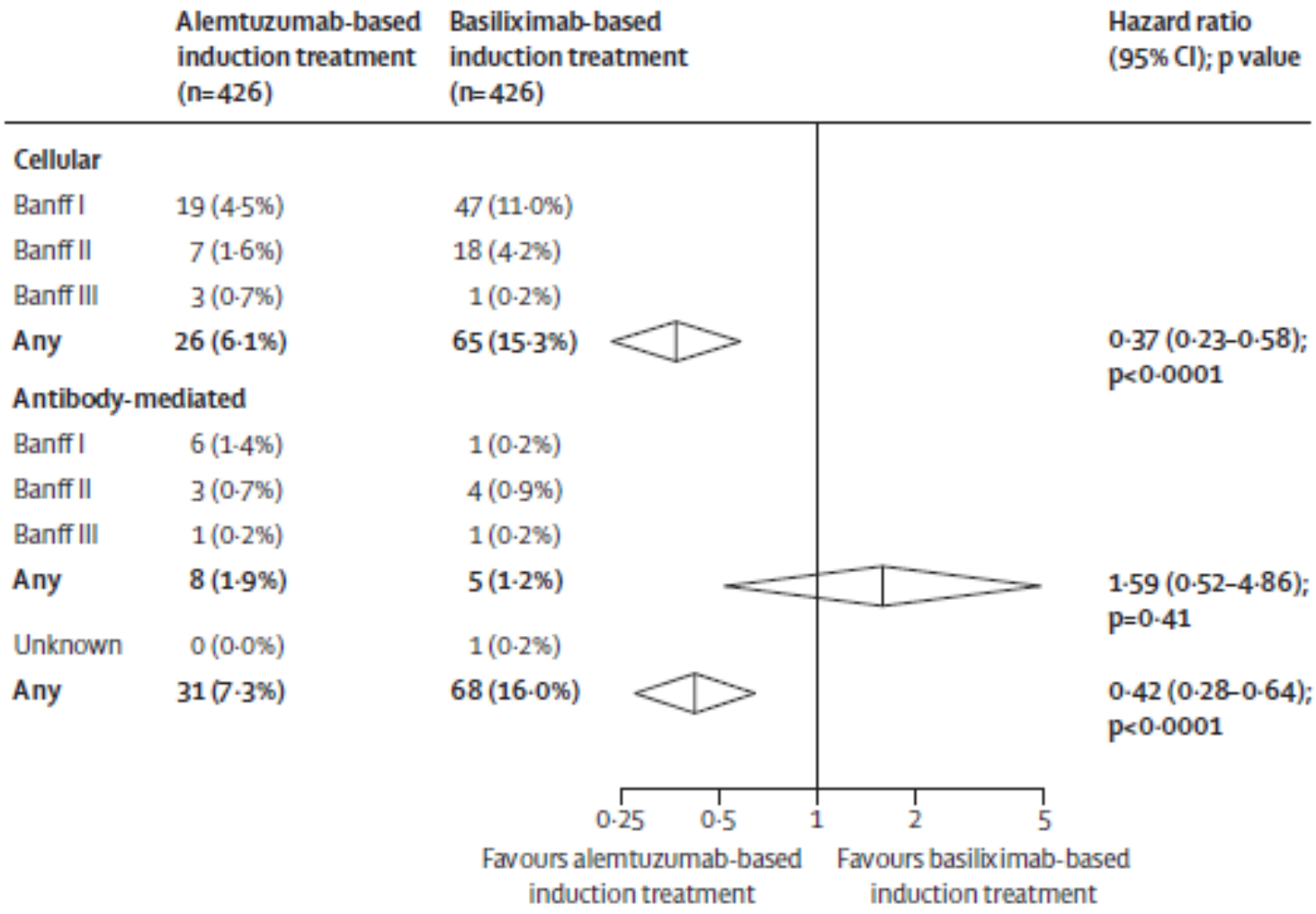
58% reduction in AR episodes in 1st 6 months with Campath

Rejection type



Serious infections (opportunistic or requiring hospital admission) in 1st 6 months

	Alemtuzumab-based induction treatment (n=426)	Basiliximab-based induction treatment (n=426)	Hazard ratio (95% CI); p value
Cytomegalovirus (CMV) infections			
CMV viraemia	24 (6%)	23 (5%)	..
CMV syndrome	10 (2%)	17 (4%)	..
Tissue-invasive disease	7 (2%)	8 (2%)	..
Other	1 (<0·5%)	0	..
Any CMV infection	39 (9%)	43 (10%)	0·91 (0·59–1·40); 0·66
BK infections			
BK viraemia	30 (7%)	12 (3%)	..
BK nephritis	5 (1%)	7 (2%)	..
Any BK virus infection	32 (8%)	17 (4%)	1·92 (1·06–3·45); 0·03
Fungal infection			
Non-invasive	7 (2%)	10 (2%)	..
Invasive	3 (1%)	3 (1%)	..
Any fungal infection	9 (2%)	13 (3%)	0·68 (0·29–1·60); 0·38
Other opportunistic infections			
Pneumocystis jiroveci pneumonia	0	2 (1%)	..
Mycobacterial	3 (1%)	0	..
Other	13 (3%)	9 (2%)	..
Any	16 (4%)	11 (3%)	..
Any opportunistic infection	81 (19%)	78 (18%)	1·06 (0·78–1·45); 0·70
Non-opportunistic serious infections			
Urinary tract	44 (10%)	55 (13%)	..
Respiratory tract	22 (5%)	22 (5%)	..
Gastrointestinal	11 (3%)	8 (2%)	..
Central nervous system	0	1 (<0·5%)	..
Other	16 (4%)	21 (5%)	..
Any other serious infections	71 (17%)	83 (20%)	0·85 (0·62–1·17); 0·33
Any serious infection	135 (32%)	136 (32%)	1·02 (0·80–1·29); 0·88

- No difference in opportunistic/ non opportunistic infections overall
- But more BK infection in Campath gp
- PTLD in 1(<0.5%) of campath gp and 3 (1%) basiliximab gp
- 11 deaths (3%) in campath group cf 6 (1%) in basiliximab gp (not significant)
- No stat significant excess of any particular cause of death in either gp

Additional Secondary outcomes reported at 6/12

- Mean trough tacrolimus level over 6 months 6.9ng/ml in Campath gp vs 8.3ng/ml in simulect gp (mean difference 1.4ng/ml p<0.00001)
- Leucopenia was more common in Campath gp (153 [36%] patients *vs* 44 [10%] patients; p<0 · 0001), but no difference in severe neutropenia (absolute neutrophil count <1 × 10^9 [7%] *vs* 25 [6%];
- No difference in the occurrence of steroid-resistant rejection (2 [1%] patients in Campath gp *vs* 5 [1%] patients I the basiliximab group; HR 0.40, 95% CI 0.08–2.04; p=0.25)
- No difference in DGF: 127 [30%] *vs* 102 [24%]; OR 1.35, 95% CI 1.00–1.83; p=0.054).
- Post hoc analyses at 12 months
  - benefit of Campath arose during the 1st few weeks and was maintained at 1 year
  - no significant difference in graft function at 6 months (mean eGFR 50 campath gp *vs* 49.8 simulect gp)

Conclusions

- Campath induction followed by reduced dose CNI and MPA and steroid avoidance approx. halves rate of AR in 1st 6 months compared to standard basiliximab therapy
- HR of 0.42 predominantly driven by large effect seen in first few weeks after tx
- No overall excess of opportunistic/serious infections with Campath (but ? More BK)
- Achieved a 17% reduction in tacrolimus exposure in Campath gp
- No difference in graft function at 6 months

Appraisal, limitations and thoughts

- Open-label trial (although central blinding maintained)
- Groups were very well matched
- Well powered
- Statistical analyses appropriate
- Short f/up reported at this time
- Applicability- All patients were generally low immunologic risk (92% first transplants and 4% highly sensitised). HLAi or ABOi not applicable
- Is the MPA dose/timing appropriate given a third of campath patients were leucopenic?
- What about ATG?