

Elective conversion to sirolimus versus continued tacrolimus in kidney transplantation (the 3C Study): results of a randomized trial

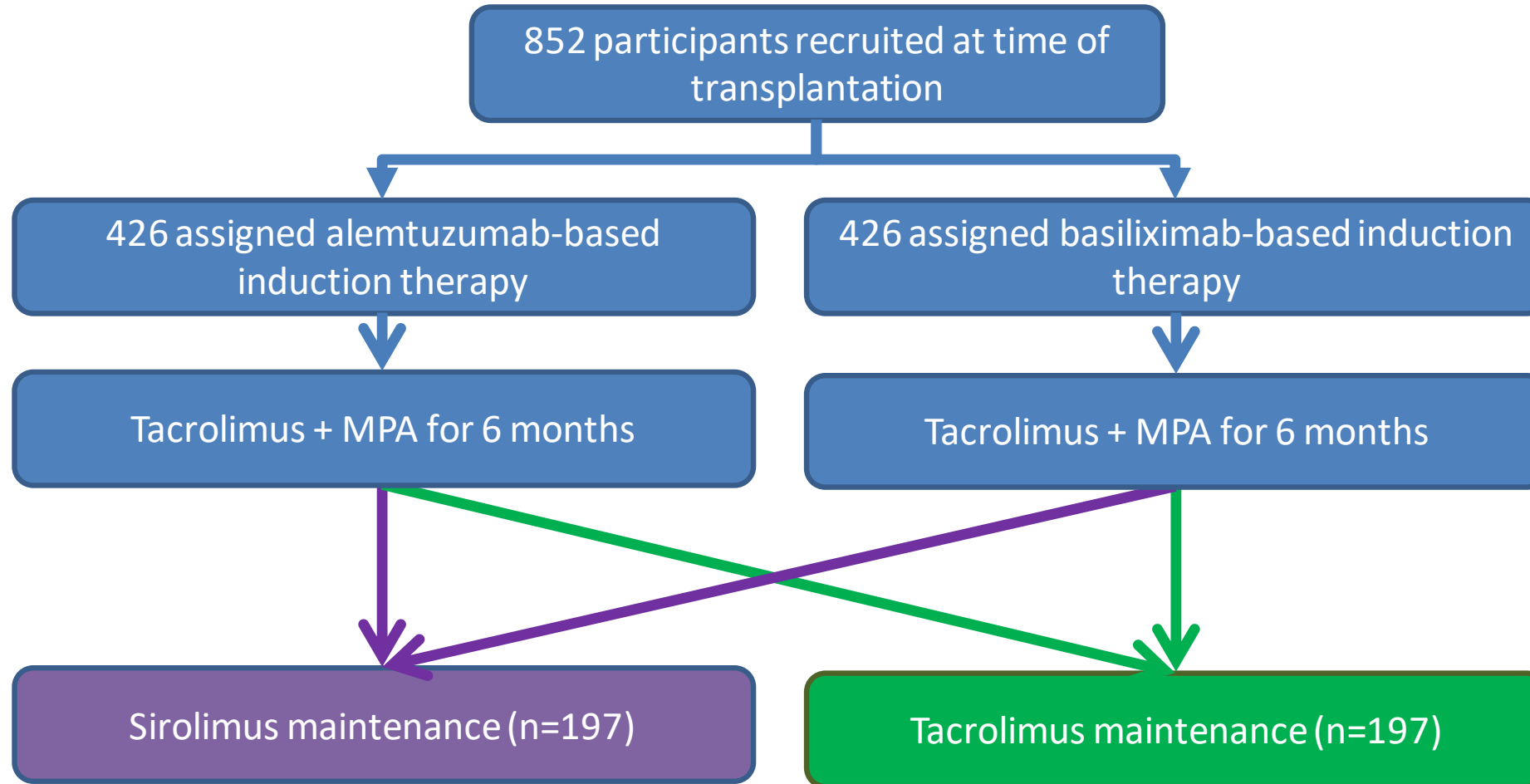
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on behalf of the 3C Collaborative Group

Background to the 3C Study

- Long-term outcomes after kidney transplantation require improvement.
- Calcineurin inhibitor (CNI) nephrotoxicity is one contributor to late transplant failure
- Strategies that minimize or avoid CNIs might improve long-term outcomes

Design of the 3C Study



Outcomes of maintenance therapy comparison (at 2 years post-transplant)

- Primary: estimated glomerular filtration rate (eGFR)
- Secondary outcomes:
 - Biopsy-proven acute rejection
 - Serious infections
 - Opportunistic
 - Other infections requiring admission

Baseline characteristics

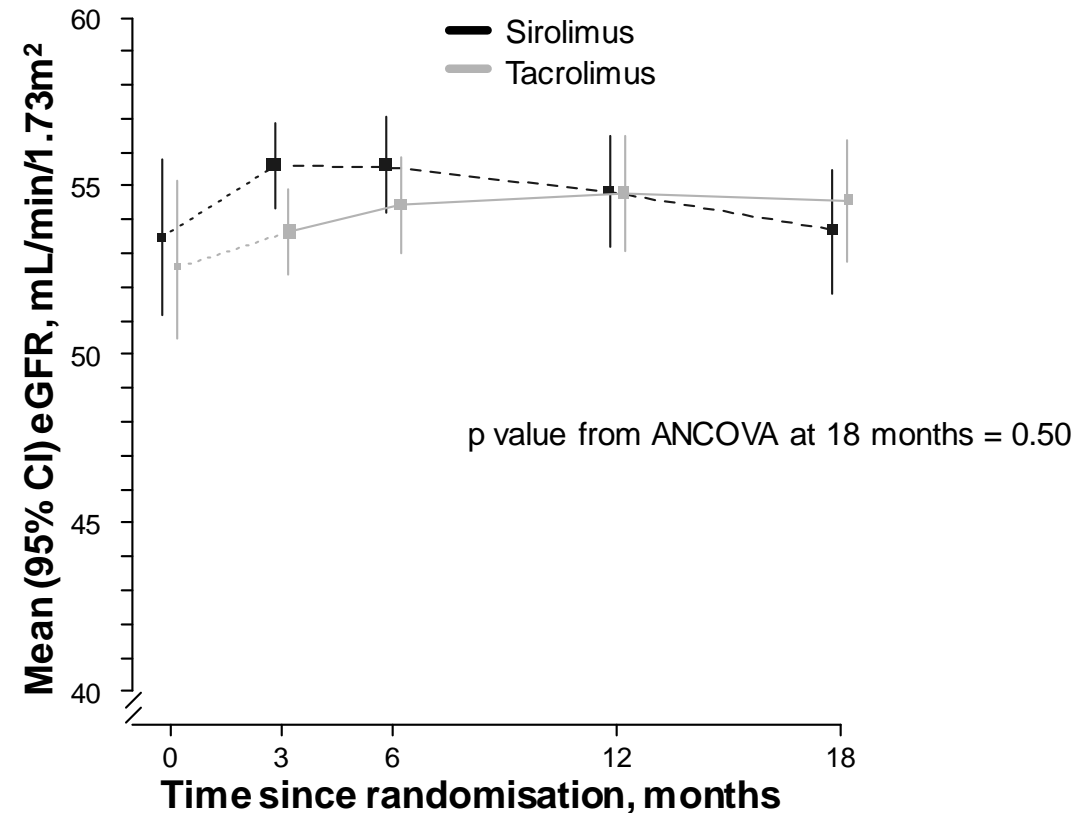
| | | Sirolimus n=197 | Tacrolimus n=197 |
|--|--------|--------------------|---------------------|
| Mean age (SD) | | 52 (13) | 52 (13) |
| Female | | 65 (33%) | 65 (33%) |
| Donor type | | | |
| | DBD | 66 (34%) | 65 (33%) |
| | DCD | 89 (45%) | 95 (48%) |
| | Living | 66 (34%) | 63 (32%) |
| Mean eGFR (mL/min/1.73m ² , SD) | | 53.5 (16.8) | 52.6 (16.6) |
| Median urine protein:creatinine ratio (mg/mmol, IQR) | | 133 (80-235) | 135 (82-228) |
| Alemtuzumab-based induction therapy | | 95 (48%) | 97 (49%) |

Compliance with treatment

| Time since randomization | Sirolimus n=197 | Tacrolimus n=197 |
|--------------------------|--------------------|---------------------|
| 3 months | 148/195 (76%) | 195/197 (99%) |
| 6 months | 132/193 (68%) | 194/197 (98%) |
| 12 months | 116/192 (60%) | 191/194 (98%) |
| 18 months | 91/188 (48%) | 180/191 (94%) |

Denominator is number of participants alive and with functioning transplant at the end of the follow-up window.

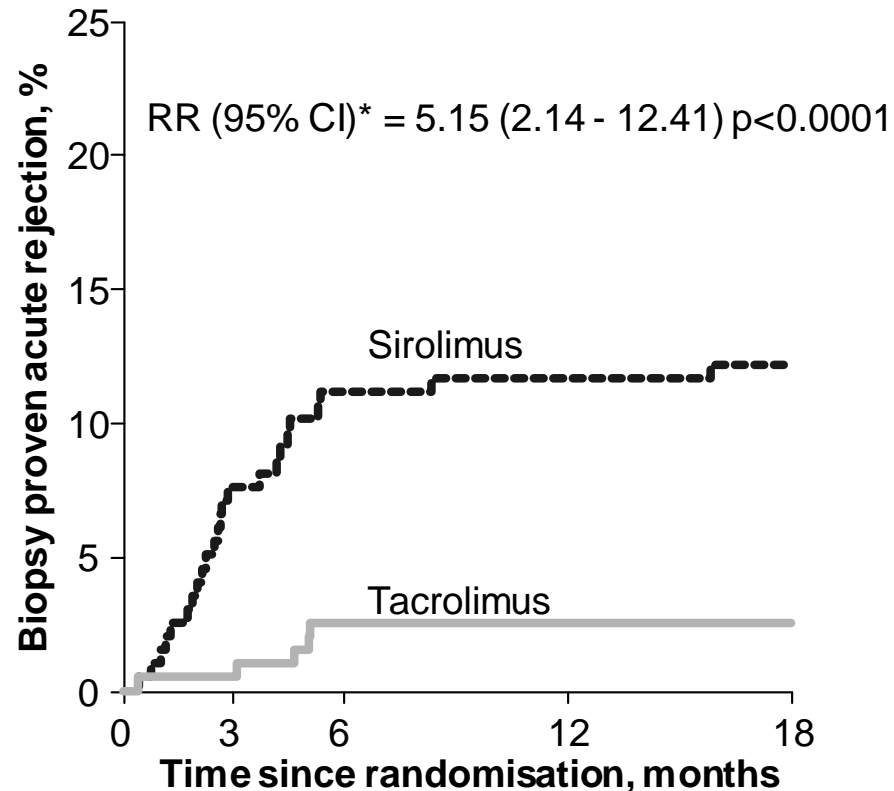
Effect of allocation to sirolimus-based maintenance therapy on transplant function over 18 months



| | Mean (SE) eGFR, mL/min/1.73m ² | | | | |
|-------------------|---|------------|------------|------------|------------|
| Sirolimus | 53.5 (1.2) | 55.6 (0.6) | 55.6 (0.7) | 54.8 (0.9) | 53.7 (0.9) |
| Tacrolimus | 52.6 (1.2) | 53.6 (0.6) | 54.4 (0.7) | 54.8 (0.9) | 54.6 (0.9) |

Follow-up mean (SE) eGFR estimates are adjusted for the values at randomisation, with any missing follow-up values imputed using multiple imputation. Mean (SE) estimates at randomisation are unadjusted.

Effect of allocation to sirolimus on transplant rejection and serious infection



| Serious infection | | SRL | TAC | Rate ratio (95% CI) | p |
|------------------------------|----------|------------|------------|-------------------------|--------------|
| | Opp. | 11% | 11% | 1.00 (0.56-1.81) | 0.9 |
| | Non-opp. | 42% | 31% | 1.54 (1.11-2.15) | 0.01 |
| Any serious infection | | 48% | 35% | 1.51 (1.11-2.06) | 0.008 |

Number at risk

| | | | | | |
|-------------------|-----|-----|-----|-----|-----|
| Sirolimus | 197 | 182 | 175 | 174 | 173 |
| Tacrolimus | 197 | 196 | 192 | 192 | 192 |

* RR was derived from a Cox regression model

Summary and acknowledgements

- Allocation to sirolimus did not improve transplant function at 18 months
- Increased risk of rejection and serious infection
- Longer-term follow-up underway
- Funded by NHS Blood & Transplant, Pfizer and Novartis
- With thanks to participants and local research staff