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Thymoglobulin Versus Alemtuzumab Versus Basiliximab Kidney Transplantation From Donors After Circulatory Death

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Introduction: The Campath, Calcineurin inhibitor (CNI) reduction, and Chronic allograft nephropathy (3C), a study comparing alemtuzumab versus basiliximab induction immunosuppression in kidney transplants, has found lower acute rejection rate with alemtuzumab but same graft survival. The aim of the current study is to evaluate the effect of induction immunosuppression (thymoglobulin, alemtuzumab, basiliximab) on the outcome of kidneys of donors after circulatory death (DCD).

Methods: Data of the 274 DCD patients of the 3C obtained from the sponsor were compounded with the 140 DCD patients who received thymoglobulin in a single center with the same entry criteria as the 3C, giving 414 patients on 3 induction regimes.

Results: There were more male donors ($P < 0.05$) and human leukocyte antigen and DR mismatched patients in the thymoglobulin group ($P < 0.001$). Death-censored graft survival at 6 months was 98.6% in the thymoglobulin, 95.5% in the alemtuzumab ($P = 0.08$), and 95.7% in the basiliximab group ($P = 0.09$) and at 2 years 97.9% versus 94.8% ($P = 0.13$, hazard ratio [HR] 2.8, 95% CI 0.7–10.9) versus 94.3% ($P = 0.06$, HR 3.5, 95% CI 0.9–13.6), respectively.
The 2-year overall graft survival was 95% in the thymoglobulin versus 88% in the alemtuzumab (unadjusted $P = 0.038$, adjusted HR 2.4, 95% CI 0.99–5.9) and 91.4% in the basiliximab group ($P = 0.21$). The 2-year patient survival was numerically less in the alemtuzumab compared with the thymoglobulin group (91.8% vs. 97.1%, $P = 0.052$, HR 2.90, 95% CI 0.93–9.2). Acute rejection was 17% in the basiliximab, 4.3% in the thymoglobulin, and 6% in the alemtuzumab group ($P < 0.001$).

Conclusion: In DCD transplants, thymoglobulin induction may provide advantage over alemtuzumab in patient survival and the same advantage as alemtuzumab over basiliximab in terms of acute rejection. Differing maintenance immunosuppression may contribute to the difference found.

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Kidney transplantation is the preferred form of renal replacement therapy for most, appropriately selected, patients with end-stage renal failure. A shortfall of standard criteria donors, compared with the number of recipients who would benefit from transplantation, has led to the increasing use of different types of deceased donors (increased expanded criteria donors after brain death, DCD, donors with positive hepatitis C virology, very old donors aged >75 years). In the United Kingdom, transplants from DCD represent almost 30% of all transplants performed.[1]

Although initially DCD kidneys were restricted to relatively younger donors, this is no longer the case.[2–4] Over time, there have been major improvements in DCD kidney transplant outcomes, comparable with DBD transplants.[5] A higher proportion of those kidneys are affected by delayed graft function (DGF).[4,6,7] DGF has been associated with poorer long-term graft outcomes and, at least in some studies, with an increased risk of rejection.[8,9] Induction strategies are likely to be one of the tools for clinicians to decrease the risk of DGF,[10] along with organ preconditioning, perfusion technology, and *ex vivo* manipulation. Tacrolimus, the most often used maintenance

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immunosuppression of choice might exaggerate DGF despite its excellent safety and efficacy profile.[11]

Immunosuppression strategies that minimize CNI exposure are therefore of interest.[12] One such strategy is to use more potent induction therapy at the time of transplantation, to minimize CNI exposure from the time of transplantation, without increasing the risk of rejection.[13–17]

The 3C study[18] did exactly that, comparing the efficacy and safety of an induction therapy strategy of alemtuzumab with reduced CNI exposure, with a nondepleting antibody induction (basiliximab) with standard CNI exposure. This study included all types of kidney transplants and revealed a significant reduction of the rejection rate in the alemtuzumab arm compared with the basiliximab arm but no difference in survival or kidney function at 6 months and 2 years post-transplant.[19] Interestingly, there was a trend for increased DGF in the patients treated with alemtuzumab (although this did not reach statistical significance).

Basiliximab (Simulect, Novartis Basel, an interleukin-2 receptor monoclonal antibody), alemtuzumab (Campath, Sanofi-France, a CD52 depleting monoclonal antibody), and rabbit thymoglobulin (Sanofi-France, a polyclonal antibody) are the 3 most often used induction agents worldwide.

Studies have revealed that thymoglobulin allows safe minimization or delayed introduction of CNIs without negatively affecting the rate of rejection.[14,20–22] In addition, it has other effects, not associated with its lymphocyte-depleting properties, including inhibition of leucocyte migration and adhesion molecules, induction of complement mediated mechanisms, and ability to inhibit certain lymphoid cell receptors.[23] In animal studies, it has been found to reduce ischemia-reperfusion injury, expected to be more severe in DCD kidneys owing to the period of warm ischemia that occurs on retrieval.[24,25] After the result of those and other clinical and experimental studies, we postulated that thymoglobulin might have a specific beneficial effect on DCD kidney transplants by maintaining a low rejection rate, but also by allowing reduced CNI exposure and reduction of ischemia-reperfusion injury improving both short- and long-term outcomes.

Given the paucity of large series of data in DCD kidneys comparing different induction agents (combined with either standard or reduced exposure to CNIs), we carried out this cohort study by combining the raw data of the DCD transplants from the 3C multicenter study with, prospectively collected data of, DCD kidney recipients who received induction with thymoglobulin in a single center.

Given that an adequately powered prospectively randomized study in DCD only kidney transplants is unlikely to occur, the current study represents a valuable source of information.

METHODS

Design

The methodology of the 3C study has been published in detail elsewhere.[18] Raw data of the cohort of DCD recipients ($n = 274$) of the 3C study who received either alemtuzumab or basiliximab as induction agent were obtained from the sponsor of the investigation trial (Oxford Clinical Trials Unit) that included patients from our center. Prospectively collected data of all patients who received thymoglobulin induction for DCD kidneys (standard of care) in a single center (140 participants) with similar entry criteria as the 3C were included in the analysis, giving a total of 414 patients. The latter prospectively collected data included patients both before and after the 3C study recruitment period (reducing the potential bias of transplant year). Patients who received thymoglobulin during the recruitment period of 3C were excluded from analysis to avoid potential selection bias. There were only 8 eligible patients with DCD grafts who did not receive thymoglobulin as a result of frailty during this period. Patients who received at least a single dose of either alemtuzumab, thymoglobulin, or basiliximab were included.

Allocation of DCD kidneys was according to the national UK policy of the time. From 2004 to 2007, this initially allocated both DCD kidneys of a single donor to the closest transplant center. This policy changed during the course of the study to follow changes to the national allocation program with more DCD kidneys shared nationally after a point algorithm.

The primary outcomes were graft survival and death censored at 6 months and at 2 years. At 6 months, patients in the 3C study were offered a second randomization to sirolimus or continuation of tacrolimus. Given that a significant proportion of patients did not proceed to second randomization and the inferior outcome of the maintenance phase of the 3C study as regards to the arm converted to sirolimus, the post-6 months data of the current study were interrogated further to account for the effect of this maintenance phase treatment.

Maximum follow-up time was to 2 years owing to the lack of validated information thereafter for the 3C participants.

Patient survival, overall survival, and acute rejection were secondary efficacy outcomes. The occurrence of cytomegalovirus infection, *Pneumocystis jiroveci*

pneumonia and post-transplant lymphoproliferative disease (PTLD) was also compared among the groups and represented the main safety outcomes.

Recipients in the thymoglobulin arm were assigned to receive a daily dose of 1.25 mg/kg rabbit thymoglobulin (rounded to the closest 25 mg) in 5 consecutive days. The maximum individual daily dose was 125 mg. Recipients who participated in other clinical trials during this period were excluded from the study (none of these studies involved ATG induction). Thymoglobulin, in common with the 3C entry criteria, was contraindicated in the following circumstances (day 0): white blood cell count $<2 \times 10^9$/l, platelets $< 75 \times 10^9$/l, or previous PTLD. The initial and subsequent infusions were administered by a central venous catheter in 4 to 6 hours. Patients received maintenance immunosuppression with tacrolimus 0.05 mg/kg/d into 2 divided doses aiming for a low trough level of between 4 and 7 ng/ml. In the presence or anticipation of DGF, tacrolimus was freely omitted in the first 5 days at the discretion of the team and subsequently reintroduced with the above-mentioned dose in all recipients. Patients also received up to 1 g of mycophenolate mofetil in 2 divided doses per day (median dose 1.5 g) and oral prednisolone. Prednisolone was administered at 20 mg for 4 weeks and subsequently tapered in 2-week intervals by 5 mg until withdrawn (at 3 months).

Routine prophylaxis against *P jiroveci* pneumonia with co-trimoxazole was given for 6 months. Anticytomegalovirus prophylaxis with valganciclovir was provided if the donor and/or recipient had seropositive results.

Summary of 3C Study Protocol

In the basiliximab arm, patients received mycophenolate sodium 540 to 720 mg twice daily (or mycophenolate mofetil equivalent) in combination with tacrolimus to achieve tacrolimus levels of 5 to 12 ng/ml in the first 6 months and 5 to 7 ng/ml subsequently. Prednisolone was started at 20 mg and withdrawn according to local protocols.

In the alemtuzumab arm, patient received 360 mg twice daily of mycophenolate sodium (or mycophenolate mofetil equivalent) in combination with tacrolimus to achieve levels of 5 to 7 ng/ml without steroids. Patients randomized post-6 months to sirolimus aimed for sirolimus levels of 5 to 10 ng/ml.

Diagnosis of Rejection

All recorded episodes of rejection were biopsy proven according to the Banff classification of 2015 (and included borderline changes for rejection).

Definition of DGF

DGF was defined as dialysis requirement in the first week. Cases where the cause of delayed function was later found to be thrombosis were excluded from being reported as DGF.

There was no requirement for histologic confirmation of acute tubular necrosis. In nonrecovering acute tubular necrosis protocol, biopsies were required at 3 weeks to exclude rejection.

Statistical Analysis

Data analysis was carried using SPSS version 25 and GraphPad Prism version 6. Time was recorded as a continuous variable. Most of the potential confounding variables are categorical, banded variables. The relationships between these variables and the outcomes are quantified through proportions with the χ^2 test used to detect any significant differences. Those variables that are continuous are compared with the outcomes through means and CI with possible significant differences identified through t test. A $P < 0.05$ was used for any difference to be deemed significant. Graft survival was presented as censored and noncensored for death. Cumulative survival at various time points was calculated using the Kaplan-Maier life table analysis and compared among induction groups with the log rank method. The HR and 95% confidence limits were used to demonstrate or refute the magnitude of the effects. Cox regression was used to model the outcomes in terms of time with and without adjustment for those risk factors deemed significant.

RESULTS

Patient Demographics

A total of 414 recipients of DCD kidneys were available for analysis among the 3 groups: 140 in the thymoglobulin, 140 in the basiliximab, and 134 in the alemtuzumab arm.

Baseline characteristics of donors and recipients are presented in Table 1. There was no difference in donor and recipient ages between the 3 groups. There were more male donors in the group who received thymoglobulin, although information on donor sex from the 3C data was incomplete. There were significantly more total human leukocyte antigen and DR mismatched transplants within the thymoglobulin group compared with both the basiliximab and the alemtuzumab group ($P < 0.05$ for both comparisons). There was no difference in the cold ischemic times or primary warm ischemia among the groups and neither on the incidence of diabetes mellitus.

Table 1. Patient demographics in the 3 induction groups

Induction type	Thymoglobulin (140)	Alemtuzumab (134)	Basiliximab (134)	*P*
Donor age mean (95% CI for mean)	49.7 (47.1–52.35)	48.4 (45.3–51.5)	48.3 (45–51.6)	0.76
Donor sex M/F (%)	99/41 (70.7/29.3)	79/49 (59/36.6) 6 missing (4.5%)	72/53 (51.4/37/9) 15 missing (10.7%)	0.5
Recipient age mean (95% CI for mean)	53.6 (51.6–55.6)	52.4 (50.3–54.4)	51.9 (50–53.8)	0.46
Recipient sex M/F (%)	101/39 (72.1/27.9)	91/43 (67.9/32.1)	99/41 (70.7/29.3)	0.7
CIT in h mean (95% CI for mean)	13.1 (12.37–13.9)	13.3 (12.37–14.28)	12.4 (11.53–13.39)	0.36
DR mismatch 0/1 or 2 (%)	25/83/32 (17.9/59.3/22.9)	38/79/17 (28.4/59/12.7)	44/78/18 (31.4/55.7/12.9)	<0.001
Total HLA mismatch 0/1–4/5–6 (%)	1/105/34 (0.7/75/24.3)	3/112/19 (2.2/83.6/14.2)	3/114/20 (2.14/81.43/14.3)	<0.001
Diabetes as cause of ESRF (%)	14 (10%)	15 (11.1)	14 (10)	0.84

CIT, cold ischemic time; DR, DR isotype; ESRF, end-stage renal failure; F, female; HLA, human leukocyte antigen; M, male.
There were more patients with 1 or 2 HLA-DR mismatches and 1 to 4 and 5 to 6 total HLA mismatches among the patients who received thymoglobulin compared with those who received either alemtuzumab or basiliximab.

Graft Survival

Death-censored graft survival at 6 months was 98.6% in the thymoglobulin compared with 95.5% in the alemtuzumab ($P = 0.08$) and 95.7% in the basiliximab group ($P = 0.09$).

Death-censored graft survival at 2 years was 97.9% in the thymoglobulin compared with 94.8% in the alemtuzumab ($P = 0.13$, adjusted HR 2.8, 95% CI 0.7–10.9) and 94.3% in the basiliximab group ($P = 0.06$, adjusted HR 3.5, 95% CI 0.9–13.6) (Figure 1).

The 2-year overall graft survival was 95% in the thymoglobulin compared with 88.1% in the alemtuzumab group ($P = 0.038$) and 91% in the basiliximab group (thymoglobulin vs. basiliximab $P = 0.21$). Using Cox regression to allow the effect of other variables on the determination of differences between thymoglobulin and alemtuzumab, we get $P = 0.052$, adjusted HR 2.4, 95% CI 0.99–5.9 (Figure 2).

Graft Survival in Tacrolimus-Based Maintenance Patients

Given the caveats described in the Methods section, an exploratory further analysis was performed where patients who were assigned to sirolimus treatment within the 3C study DCD cohort were excluded. After exclusions, there were 140 patients in the thymoglobulin arm, 105 in the alemtuzumab arm, and 112 in the basiliximab arm available for this further analysis after 6 months.

The 2-year graft survival censored for death was 97.9% in the thymoglobulin group versus 93.3 in the alemtuzumab group and 92.9% in the basiliximab group (thymoglobulin vs. alemtuzumab $P = 0.07$, thymoglobulin vs. basiliximab $P = 0.05$).

Patient Survival

The 2-year patient survival in the thymoglobulin group (97.1%) was numerically better compared with

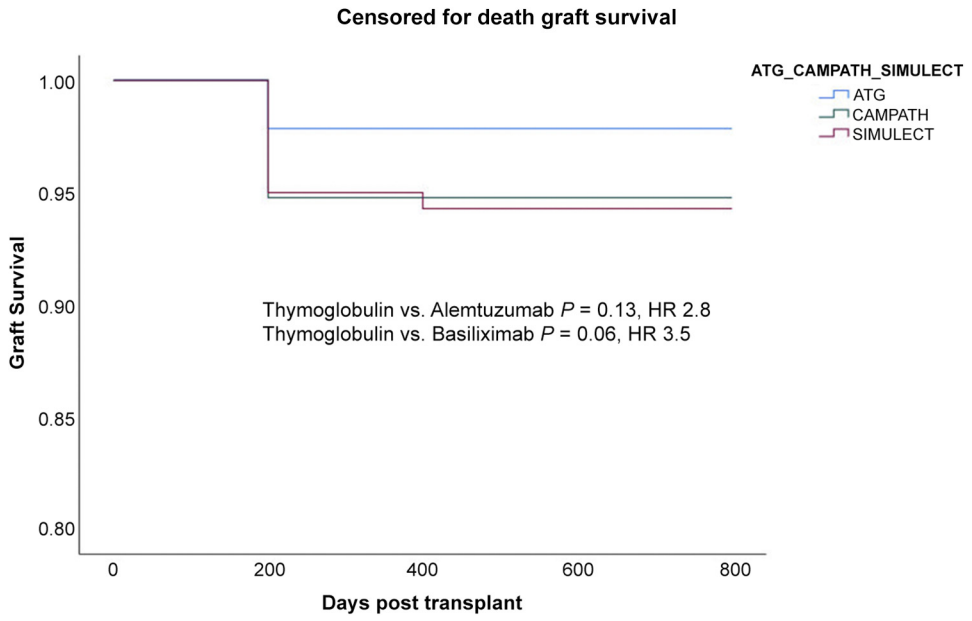

Figure 1. Death-censored graft survival. The death-censored graft survival at 2 years was 97.9% in the thymoglobulin compared with 94.8% in the alemtuzumab ($P = 0.13$, adjusted HR 2.8, 95% CI 0.7–10.9) and 94.3% in the basiliximab group ($P = 0.06$, adjusted HR 3.5, 95% CI 0.9–13.6). HR, hazard ratio.

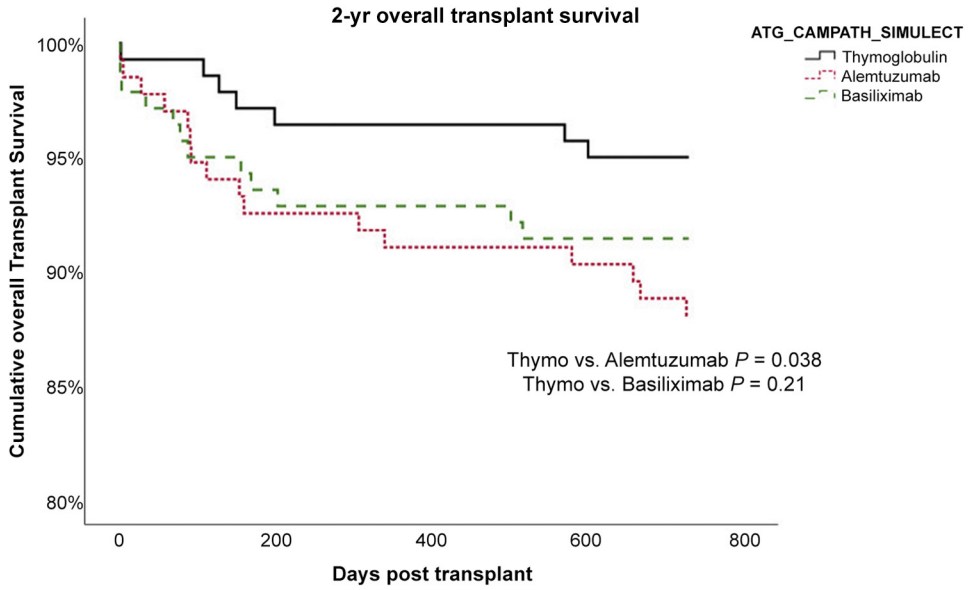

Figure 2. Overall graft survival. The 2-year overall graft survival, was 95% in the thymoglobulin compared with 88% in the alemtuzumab group (unadjusted $P = 0.038$, adjusted HR 2.4, 95% CI 0.99–5.9) and 91% in the basiliximab group (thymo vs. basiliximab $P = 0.21$). HR, hazard ratio; Thymo, thymoglobulin.

the alemtuzumab group (91.8%, $P = 0.052$, HR 2.90, 95% CI 0.93–9.2) and similar to the basiliximab group (96.4%, $P = 0.72$) (Figure 3). Results were similar in the tacrolimus-only recipients.

Acute Rejection

There were more patients with biopsy-proven acute rejection at 1 year in the basiliximab arm (24 patients, 17.1%) compared with either the thymoglobulin (6 patients, 4.3%, odds ratio 4.6, 95% CI for odds ratio 1.8–11.69, $P < 0.001$) or the alemtuzumab group (8 patients, 6%, odds ratio 3.26, 95% CI for odds ratio 1.4–7.5, $P < 0.001$).

Delayed Graft Function

The DGF was numerically higher in the thymoglobulin group (58.6%) compared with the alemtuzumab (46.3%) and the basiliximab group (43.6%).

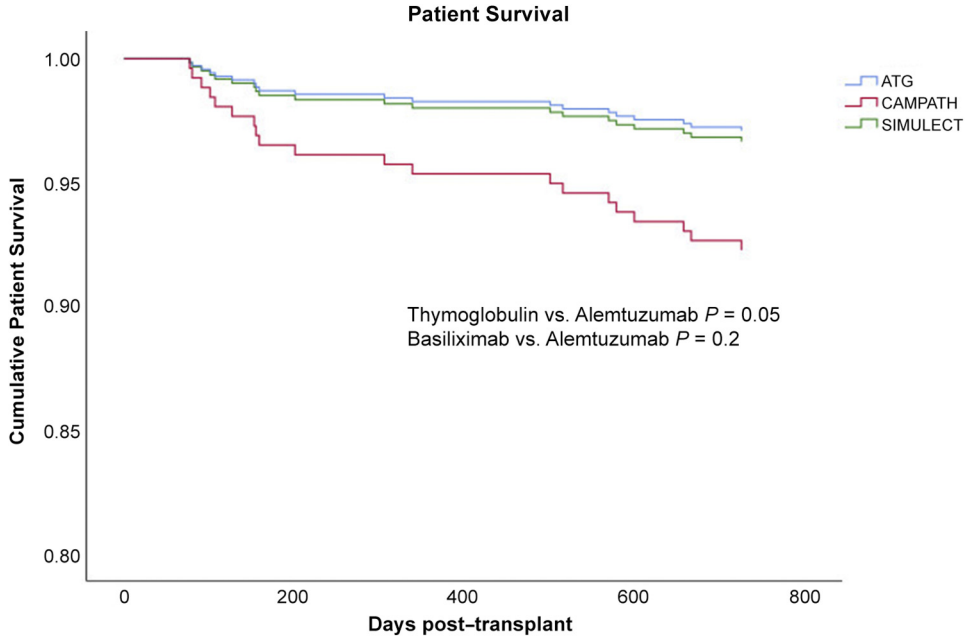

Figure 3. Patient survival. The 2-year patient survival in the thymoglobulin group (97.1%) was better compared with the alemtuzumab group (91.8%, $P = 0.05$, HR 2.90, 95% CI 0.93–9.2) and similar to the basiliximab group (96.4%, $P = 0.72$). The difference between basiliximab and alemtuzumab was nonsignificant ($P = 0.2$). HR, hazard ratio.

Tacrolimus Levels

In the thymoglobulin group, 90% of the patients were within the specified range at 6 months (mean 5.9 μg/l) and at 12 months (mean 5.6 μg/l) compared with 7.4 μg/l and 7 μg/l in the 3C arms at 3 and 18 months, respectively.

Safety

The white blood cell count at 6 months was 6.6 (SD 2.54) in the basiliximab group compared with 5.2 (SD 2.23, $P = 0.01$) in the alemtuzumab and 5.85 (SD 2) in the thymoglobulin group ($P = 0.16$ vs. basiliximab and $P = 0.06$ vs. alemtuzumab).

Cytomegalovirus infection was 7.9% in the thymoglobulin, 7.5% in the alemtuzumab, and 8.6% in the basiliximab group ($P = 0.8$).

There was no difference in the incidence of PTLD among the 3 groups (2 vs. 2 vs. 1) and no difference in *P jiroveci* pneumonia infections (0 vs. 0 vs. 1).

DISCUSSION

This study reveals that a thymoglobulin-based induction combined with low tacrolimus levels results in numerically better censored for death graft survival at 2 years post-transplant compared with an alemtuzumab and to a basiliximab-based regime. High HRs of the 2 latter regimes, with confidence levels skewed to the right, point toward a real effect. Thymoglobulin induction seems also to be associated with better patient survival compared with alemtuzumab at 2 years post-transplant.

Both alemtuzumab and thymoglobulin reduced the chance of rejection by approximately two-thirds compared with basiliximab, revealing a similar trend to the results seen between alemtuzumab and basiliximab in the 3C study among all transplants.[18,19] This is particularly important during the COVID-19 era when re-attendance for rejection treatment introduces new risks.

As a result of these outcomes combined, a higher proportion of thymoglobulin patients remained free of acute rejection, graft failure or death combined, compared with those in the alemtuzumab and basiliximab groups. This is in common with data of thymoglobulin versus basiliximab from the 1010 trial.[26]

To our knowledge, this is the first large-scale study revealing the superiority of thymoglobulin in the context of a wide range of controlled DCD kidney transplants. Despite not being a randomized study between thymoglobulin and the 3C groups, the very broad eligibility criteria of patients allowed for similar baseline characteristics. Moreover, the patients in the thymoglobulin group had a significantly worse overall human leukocyte antigen and DR mismatch with their donors. Donor age, cold ischemic times, and diabetes are the most relevant risk factors for outcome in DCD transplants[3,7,27] and were similar in all groups. The survival analysis was performed unadjusted and adjusted to account for potential confounding risk factors. A previous smaller-cohort single-center study had also found an advantage of thymoglobulin over alemtuzumab at 3 years survival, in the context of DBD and LD nonsensitized kidneys.[28] The larger INTAC study[29] revealed that censored for death graft survival was the same between alemtuzumab and thymoglobulin in a high-risk group.

The 2-year overall results of the 3C study revealed inferiority of the sirolimus conversion in terms of late rejection. This could have affected the 2-year results of the two 3C induction regimes in this study. The separate exploratory analysis of only patients who were continued on tacrolimus excluded to a great degree this potential bias. The 2-year graft survival difference between the thymoglobulin and the alemtuzumab arm remained essentially the same in the subgroup that received tacrolimus maintenance whereas the difference did increase between thymoglobulin and basiliximab.

The reduction in the rejection rate in the thymoglobulin and alemtuzumab groups compared with the basiliximab group was roughly equivalent; therefore, this is unlikely to account for the difference observed in survival between the 2 depleting agents. This could account though for the difference found between thymoglobulin and basiliximab in the death-censored survival data. The higher number of deaths in the alemtuzumab compared with the thymoglobulin group is a significant finding. We are conducting an analysis of death causality, both in the short and the long terms, to clarify this point further.

A center effect is possible and cannot be fully excluded with the present data. With the unique combination of very low initial tacrolimus level, covered by the effect of thymoglobulin, the anti-inflammatory effect of steroids, and avoidance of steroids, long-term side effects might be indeed the underlying reason for the improved results. It is unlikely that given the wide eligibility of both the 3C study and the thymoglobulin group that there is an inherent selection bias. It is worth noting that the transplant center that recruited the thymoglobulin patients was also the second highest recruiter for the 3C study further reducing the possibility of solely a center effect. The safe early withdrawal of steroids under thymoglobulin induction was also previously found in a randomized multicenter study reported by Woodle *et al.*[30] in living donor transplants and confirmed here in DCD transplants.

Another hypothesis is that either the magnitude or the type of the DGF could account for these differences.[31] The DGF rate though, defined as at least 1 dialysis session during the first week post-transplant, was higher in the thymoglobulin arm. The difference in the threshold for dialysis between centers and the lack of data on the drop of creatinine during the first week did not allow us to perform a more valid comparison. DGF in DCD kidneys is of different nature to the one observed in DBD kidneys.[31–33] It is conceivable that thymoglobulin in contrast with alemtuzumab might prevent the more serious form of ischemia-reperfusion injury that leads to early failures. The difference found in graft survival at 6 months might be a result of that. A separate preliminary study of ours within the thymoglobulin induction group has revealed that the DGF rate in this group was significantly lower in patients who received a total of at least 5 mg/kg of thymoglobulin compared with lower doses,[34] lending some support to that hypothesis.

A significant concern with the use of depleting antibodies is their potential to increase the risk of serious infections and PTLD. Complementing the 3C study findings regarding alemtuzumab: neither alemtuzumab nor thymoglobulin seems to increase significant opportunistic infections, including cytomegalovirus and *P jiroveci* pneumonia, nor to increase PTLD compared with basiliximab at least as part of those maintenance regimes. The overall burden of immunosuppression might be what affects those results. Both alemtuzumab and thymoglobulin groups were run on lower tacrolimus levels, avoided extra treatment for rejection, and either avoided maintenance steroids (alemtuzumab group) or had steroids withdrawn by 3 months (thymoglobulin group).

Earlier thymoglobulin studies found an increased rate of PTLD. In contrast, Opelz and Döhler[35] registry data reveal no correlation between thymoglobulin and increased PTLD rate in the early postoperative years. Our study confirms that thymoglobulin combined with low level maintenance immunosuppression is associated with low levels of PTLD (1.5%) at 2 years.

A valid concern with the current study is that it took the raw data from a randomized study and combined it with prospectively collected data from a distinct patient cohort. Although this could introduce potential for bias, the inclusion criteria for all patient groups were similar. This was verified by comparing the baseline characteristics that were evenly distributed, apart from the degree of human leukocyte antigen matching that disadvantaged the thymoglobulin group. Some of the additional variables (potential confounders) were accounted for by the multivariable Cox regression analysis. Cohort studies with strict procedures for analysis are a valuable source of information.[36,37] Eligibility criteria and outcome assessments can be standardized as in the current analysis. Such studies can still establish time and directionality of events. What they cannot do is fully exclude the possibility that the intervention effect is due to a hidden confounder.[38]

A randomized study is unlikely to occur within the DCD cohort to confirm these findings given that at least 2 recent large-scale studies in UK with different pharmacologic agents (seeking recruitment among a larger potential population of both DCD and extended DBD donor kidneys) had to stop prematurely owing to lack of recruitment.

This cohort study provides strong evidence to reveal that, in DCD kidney transplantation, thymoglobulin induction allows for low-maintenance tacrolimus treatment, with excellent 2-year outcomes that surpass those of alemtuzumab.

DISCLOSURE

The 3C Study was designed, conducted, and analyzed by the CTSU at Oxford University, and the study was funded by grants from the National Health Service Blood and Transplant Research and Development program, Pfizer, and Novartis UK. The CTSU and the lead investigator of the 3C provided access to the raw data for the DCD recipients who received alemtuzumab or basiliximab but had no input in the current analysis. The data for the current study were prospectively collected with the help of an educational grant from Genzyme UK, now part of Sanofi, France, and departmental research resources of the Cardiff Transplant Unit. None of the pharmaceutical companies had access to or influenced the current study analysis and writing. The writing group has full access to all data and accepts full responsibility for the content of this article.

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DATA SHARING STATEMENT

Full data are freely available.

AUTHOR CONTRIBUTIONS

AA conceptualized and designed the study, analyzed the data, and wrote the manuscript. TS collected and validated the data and edited the manuscript. WJW provided statistical input and analyzed the data. UK, MS, and SG edited the manuscript. LS collected the data and edited the manuscript. RC codeveloped and edited the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

STROBE Statement.

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