ORIGINAL ARTICLE

Alemtuzumab dose adjusted for body weight is associated with earlier lymphocyte repletion and less infective episodes in the first year post renal transplantation – a retrospective study

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SUMMARY

The optimal dose of alemtuzumab for renal transplant induction is not known, and the doses reported in the literature vary. This study compares two separate dosing regimens of alemtuzumab in renal transplantation. The first is a standard fixed dose of 30 mg (SD), and the second is a dose adjusted for body weight at 0.4 mg/kg (AD). In this first year post-transplant, there was no difference in patient [HR 0.64 (0.22–1.86), $P = 0.39$] or allograft survival [HR 1.18 (0.48–2.90), $P = 0.72$] between the two groups. There was also no difference in overall rejection-free survival [HR 1.12 (0.79–1.58), $P = 0.53$]. However, absolute lymphocyte count was significantly higher at all measured time points in the first year in the AD group. There were also less episodes of urosepsis [HR 1.38 (1.03–1.85), $P = 0.037$] and fungal infection [HR 5.15 (2.00–13.28), $P = 0.015$] in the AD group compared with the SD group. This study shows that AD alemtuzumab is associated with earlier lymphocyte repletion and less infective episodes in the first year postrenal transplant, without increasing the risk of rejection. This work highlights the need for studies into the optimal dosing of monoclonal antibodies used in transplantation.

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Introduction

Organ transplantation led the field in monoclonal antibody (mAb) use for clinical application, when muromab (OKT3®) became the first approved mAb for human use in 1986[1]. Since that time, the growth of monoclonal antibodies approved to treat a whole spectrum of diseases has continued to grow in an exponential manner, with an estimated availability of 70 different mAbs expected by 2020. [2]. There are considerable benefits of using mAbs in clinical medicine, as they mechanistically provide a more targeted approach which should improve efficacy, whilst minimizing unintentional adverse events. Although OKT3 was subsequently withdrawn, mAbs have continued to play a vital role in preventing early acute transplant rejection and have contributed to the improvement of short-term allograft outcomes, and have enabled steroid-free

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maintenance immunosuppression[3,4]. The mAbs currently used as induction therapies include basiliximab (an anti-CD25 antibody) and alemtuzumab (an anti-CD52 antibody).

Optimizing the correct dose of mAbs can be complex and relates to their pharmacokinetic (PK) and pharmacodynamic (PD) properties, which in turn depends upon the target antigen, the antibody structure/isotype and elimination as well as other covariates[5–7]. The majority of mAbs on the market are dosed according to body weight, whilst in transplantation mAbs are prescribed using fixed dose regimens[7,8]. Whether fixed dosing translates into the best clinical responses at an individual level has not been explored in the mAbs used in transplantation. However, decades of studies into trying to determine the optimal dose of ATG, a polyclonal antibody used to prevent and treat rejection, has failed to deliver a conclusive answer[9–13].

In this novel study, we compare the clinical outcomes of renal transplant patients who receive either a fixed dose of alemtuzumab or a dose adjusted for body weight.

Materials and methods

Patients

This retrospective study incorporated prospectively collected data in patients who received a renal transplant at Imperial College Renal and Transplant Centre between 2005 and 2015, with at least 1-year follow-up. We included both living and deceased donor kidneys in recipients of primary renal allografts only. We excluded patients who received induction with an interleukin-2 receptor antibody and patients who received a high immunological risk transplant, which included recipients of ABO and HLA incompatible allografts. HLA incompatibility was defined as a patient with either a positive cross-match (CDC or flow cytometry) or a negative cross-match but with preformed donor specific antibodies (DSA) detected by single antigen beads alone. We excluded patients who lost their graft because of early technical failures. Outcome data on white cell counts (WCC) and their differential along with infective episodes were collected up to 1 year post-transplant.

Immunosuppression and prophylaxis against infection

All patients received alemtuzumab induction with long-term maintenance therapy consisting of tacrolimus monotherapy. Patients received 500 mg of methylprednisolone pretransplant followed by 1 week of corticosteroids only. Tacrolimus doses were initially started at 0.05 mg/kg twice a day and then adapted to achieve a trough level of 5–8 ng/ml.

Between 2005 and 2011, all patients received a standard 30 mg dose of alemtuzumab (MabCampath, Genzyme, UK) by iv infusion post-transplant. After 2011, patients received alemtuzumab which was dose adjusted for their body weight, at a dose of 0.4 mg/kg by iv infusion post-transplant, up to a maximum of 50 mg. A change in protocol was performed because of the disproportionate rates of infection seen in historic patients with low body mass.

All patients received standard cytomegalovirus (CMV) and Pneumocystis jirovecii (PCP) prophylaxis post-transplant with valganciclovir for 3 months and co-trimoxazole for 6 months, respectively. All patients received in addition at least 5 days of broad-spectrum antibiotics, which usually consisted of ciprofloxacin. Nystatin liquid was given for anti-fungal prophylaxis for a period of 6 weeks, and patients with previous TB or at high risk received isoniazid and pyridoxine prophylaxis.

Diagnosis of rejection and infection

All rejection episodes were biopsy-proven and classified using the Banff 07 Classification of Renal Allograft Pathology[14]. Patients with rejection were treated with enhancement of their immunosuppression as previously described[15]. Patients were routinely screened for DSA within our H&I laboratory at 1, 3, 6 and 12 months post-transplant, then yearly thereafter and also at times of allograft dysfunction. Patients are screened initially using LABScreen® mixed beads (One lambda, Inc., Canoga Park, CA, USA) if nonsensitized, and subsequently or primarily screened using LABScreen® single antigen beads if sensitized. We include DSA to HLA-A, HLA-B, HLA-Cw, HLA-DR, HLA-DQ and HLA-DP antigens in our study. A mean fluorescence index [MFI] of >500 by single antigen beads on two separate occasions was taken as positive.

All infection episodes were microbiologically proved. Specific definitions for the purposes of this study are as follows: urinary tract infections required the presence of >50 mm^3 white cells, with a positive pure culture growth of $>10^5$ organisms; fungal infections included positive cultures from chest, central nervous system and blood, but not urine alone; viraemic episodes (CMV, BK and Epstein-Barr [EBV]) were considered positive only if there was evidence of replicating DNA found in

blood, urine or tissue and this was associated with a change in management (e.g. reduction in immunosuppression or treatment with anti-virals).

Statistical analysis

All statistics were performed using the MedCalc statistical software package version 16.8.4 (MedCalc software, Ostend, Belgium). Comparisons of means and frequencies of normally distributed variables were made using t-tests and the Chi-squared test; nonparametric variables were analysed by the Mann–Whitney test. Kaplan–Meier survival analysis was used to calculate time of event from transplant and significance was determined by log-rank testing. Multivariate analyses were performed using Cox regression methods, unless otherwise stated. A P value < 0.05 was deemed statistically significant.

Results

A total of 888 patients were included: 544 received the standard dose (SD) alemtuzumab and 344 received adjusted dose (AD) alemtuzumab. The baseline demographics of the two groups are shown in Table 1. There was no significant difference in the number of males, noncaucasoids, recipients of deceased donor allografts and median HLA mismatch between the two groups. However, patients in the AD group were older than the SD group, with a median age of 52.4 (51.0–53.8) and 49.4 (48.2–50.5) years, respectively, $P = 0.0008$. The proportion of HLA sensitized patients in the AD group was also higher than the SD group, at 113/344 (32.8%) and 103/544 (18.9%), respectively, $P < 0.0001$. There was no difference in the median weight at transplant between the groups, at 74.0 (72.0–75.1) kg in the AD group and 74.8 (72.9–76.9) kg in the SD group, $P = 0.55$. The mean alemtuzumab dose in the AD group was 30.37 ± 6.52 mg. The lowest dose received was 16 mg, whilst the highest dose was 50 mg.

Patient and allograft outcomes

Adjusted dose alemtuzumab did not appear to impact on allograft outcomes. At 1 year post-transplant, patient survival was 98.7% and 98.0% in the SD and AD groups, respectively, $P = 0.39$ and death censored allograft survival was 97.6% and 98.0% in the SD and AD groups, respectively, $P = 0.72$. The overall rejection-free survival was 83.6% and 85.1% in the SD and AD groups, $P = 0.53$ with an AMR-free survival of 94.7% in the SD group and 95.0% in the AD group, $P = 0.86$, and a TCMR-free survival of 88.3% and 89.9%, respectively, $P = 0.47$. De novo DSA-free survival was 87.4% and 88.2% in the SD and AD groups, respectively, $P = 0.73$.

At 4 years, patient survival was 94.6% and 93.2% in the SD and AD groups, respectively, $P = 0.50$ and death censored allograft survival was 90.7% and 93.4% in the SD and AD groups, respectively, $P = 0.34$. The overall rejection-free survival was 76.2% and 75.6% in the SD and AD groups, $P = 0.61$, with an AMR-free survival of

Table 1. Patient demographics.

		Standard dose $N = 544$ (%)	Adjusted dose $N = 344$ (%)	P value
Gender	Female	177 (32.5)	124 (36.0)	0.32
	Male	367 (67.5)	220 (64.0)	
Age at transplant	Median (years)	49.4 (48.2–50.5)	52.4 (51.0–53.8)	0.0008
Ethnicity	Caucasian	251 (46.1)	141 (41.0)	0.13
	Non-caucasian	293 (53.9)	203 (59.0)	
	Afro-Caribbean	74 (13.6)	59 (10.9)	
	Indo-Asian	189 (34.7)	102 (29.7)	
	Other	30 (5.5)	42 (12.2)	
Diabetes	No	417 (76.7)	256 (74.4)	0.50
	Yes	127 (23.3)	68 (25.6)	
Type of donor	Deceased	292 (53.7)	197 (57.3)	0.33
	Living	252 (46.3)	147 (42.7)	
Pre-emptive	No	414 (76.1)	264 (76.7)	0.89
	Yes	130 (23.9)	80 (23.3)	
HLA sensitized	No	441 (81.1)	231 (67.2)	<0.0001
	Yes	103 (18.9)	113 (32.8)	
HLA mismatch	Mean	3.2 ± 1.6	3.2 ± 1.5	0.93
Weight at transplant	Median (years)	74.8 (72.9–76.9)	74.0 (72.0–75.1)	0.55
Delayed graft function	Number (%)	98 (18.0)	64 (18.6)	0.82

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92.7% in the SD group and 91.7% in the AD group, $P = 0.81$, and a TCMR-free survival of 82.0% and 82.5%, respectively, $P = 0.37$. De novo DSA-free survival was 81.5% and 85.0% in the SD and AD groups, respectively, $P = 0.36$.

White cell repletion

Comparisons of the total WCC and their subpopulations were made at 1, 2, 3, 6, 9 and 12 months post-transplant, as shown in Table 2.

Total WCC became significantly different between the two groups at the measurements made at 3 months, with the total WCC in the SD and AD group being 5.09 (4.91–5.32) and 5.50 (5.20–5.70), respectively, $P = 0.015$. This difference was seen again at 6 months, with a WCC of 5.7 (5.47–5.97) and 6.22 (5.90–6.51) in the SD and AD groups, $P = 0.005$. However, the difference was lost at 9 and 12 months. Lymphocyte count was higher at all time points in the AD group compared with the SD group. The lymphocyte count in the SD and AD group, respectively, was 0.23 (0.23–0.24) and 0.26 (0.24–0.29), $P = 0.0009$ at 1 month; 0.39 (0.37–0.40) and 0.43 (0.38–0.47), $P = 0.0087$ at 2 months; 0.60 (0.58–0.64) and 0.73 (0.68–0.80), $P < 0.001$ at 3 months; 0.90 (0.84–0.93) and 1.05 (0.97–1.14), $P < 0.0001$ at 6 months; 0.98 (0.93–1.00) and 1.20 (1.12–1.30), $P < 0.0001$ at 9 months; and 1.10 (1.03–1.14) and 1.27 (1.17–1.38), $P < 0.0001$ at 12 months, as shown in Fig. 1. Even with follow-up up to 3 years post-transplant, lymphocyte count in the AD group remained statistically higher, with the lymphocyte count at 2 years being 1.24 (1.18–1.32) and 1.40 (1.30–1.51) in the SD and AD groups, respectively, $P = 0.0039$ and at 3 years, being 1.32 (1.27–1.38) and 1.48 (1.40–1.60), respectively, $P = 0.033$. Conversely, there was no difference in neutrophil count at any time point post-transplant. Monocyte count was statically higher in the AD group up until 9 months post-transplant. The monocyte count at 1 month in the SD and AD group was 0.30 (0.29–0.32) and 0.34 (0.32–0.36), respectively, $P = 0.004$; at 2 months was 0.38 (0.36–0.39) and 0.40 (0.36–0.42), $P = 0.02$; at 3 months was 0.45 (0.44–0.47) and 0.49 (0.46–0.52), $P = 0.0012$ and at 6 months was 0.49 (0.48–0.50) and 0.50 (0.48–0.53), $P = 0.023$, respectively, in the SD and AD group.

Table 2. Comparison of the white cell count (WCC) and subpopulations by alemtuzumab dosing.

Month	SD (Median [95%CI])	Adjusted dose (Median [95%CI])	*P* value
WCC			
1	4.66 (4.46–4.91)	4.70 (4.52–4.84)	0.73
2	4.53 (4.43–4.74)	4.74 (4.56–4.86)	0.40
3	5.09 (4.91–5.32)	5.50 (5.20–5.70)	0.015
6	5.78 (5.47–5.97)	6.22 (5.90–6.51)	0.005
9	6.08 (5.92–6.32)	6.30 (6.02–6.70)	0.11
12	6.17 (5.94–6.46)	6.40 (6.10–6.59)	0.21
Lymphocyte count			
1	0.23 (0.23–0.24)	0.26 (0.24–0.29)	0.0009
2	0.39 (0.37–0.40)	0.43 (0.38–0.47)	0.0087
3	0.60 (0.58–0.64)	0.73 (0.68–0.80)	<0.0001
6	0.90 (0.84–0.93)	1.05 (0.97–1.14)	<0.0001
9	0.98 (0.93–1.00)	1.20 (1.12–1.30)	<0.0001
12	1.10 (1.03–1.14)	1.27 (1.17–1.38)	<0.0001
Neutrophil count			
1	3.87 (3.74–4.02)	3.73 (3.58–3.92)	0.18
2	3.64 (3.50–3.80)	3.56 (3.40–3.70)	0.37
3	3.73 (3.61–3.87)	3.80 (3.57–4.05)	0.60
6	4.00 (3.78–4.12)	4.20 (3.90–4.36)	0.28
9	4.26 (4.11–4.40)	4.12 (3.92–4.31)	0.57
12	4.20 (4.05–4.35)	4.04 (3.80–4.22)	0.17
Monocyte count			
1	0.30 (0.29–0.32)	0.34 (0.32–0.36)	0.004
2	0.38 (0.36–0.39)	0.40 (0.36–0.42)	0.02
3	0.45 (0.44–0.47)	0.49 (0.46–0.52)	0.0012
6	0.49 (0.48–0.50)	0.50 (0.48–0.53)	0.0023
9	0.50 (0.49–0.52)	0.53 (0.50–0.55)	0.054
12	0.50 (0.50–0.53)	0.53 (0.50–0.57)	0.30

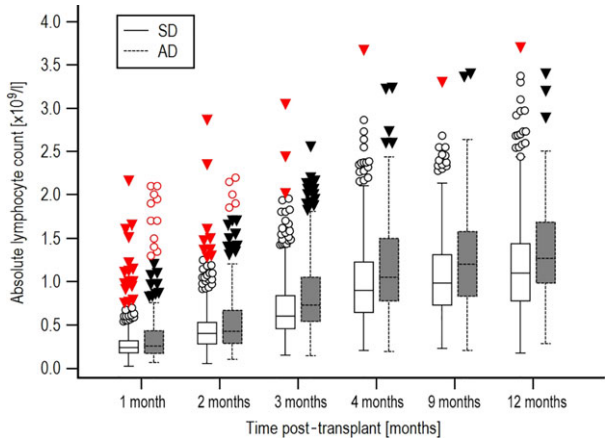

Figure 1 A comparison of lymphocyte repletion post-transplant between the standard dose and adjusted dose groups. The median absolute lymphocyte count was significantly higher at all measured time points in the first year post-transplant.

An comparison of the lymphocyte counts between those patients who had neither a rejection or infection episode compared with those who experienced either rejection or infection was made in both the SD and AD groups and can be found in Appendix S1.

Infection episodes

The overall 1-year infection-free survival between the SD and AD groups was 63.8% and 67.4%, respectively, $P = 0.14$. However, analysis of the risk factors for specific types of infections was subsequently performed and described herewith. On univariate analysis, risk factors associated with wound infection included higher body mass, with a median weight of 73.50 (72.00–75.00) kg in the patients without wound infections, compared with 81.0 (75.13–86.93) kg in patients with wound infection, $P = 0.0002$; diabetes, with 54/215(25.1%) of diabetic patients compared with 69/673 (10.3%) of nondiabetic patients experiencing wound infections, $P < 0.0001$; and receiving a deceased donor transplant, with 78/489 (16.0%) of deceased donor recipients compared with 45/399 (11.3%), $P = 0.045$ experiencing wound infections. There was a trend towards less wound infections in patients receiving AD alemtuzumab, with 84/544 (15.4%) of the SD group and 39/344 (11.3%) of the AD group developing wound infections, $P = 0.08$. On multivariate analysis, using logistical regression methods, the risk factors for wound infection, included weight [1.03 (1.02–1.04), $P < 0.0001$], diabetes [2.65 (1.74–4.04), $P < 0.0001$] and female gender [2.09 (1.39–3.26), $P = 0.001$], whilst receiving a living donor allograft [0.60 (0.40–0.92), $P = 0.018$] and AD alemtuzumab [0.61 (0.40–0.94), $P = 0.026$] appeared to negate this risk.

One-year urosepsis-free survival was inferior in the SD compared with the AD group at 76.4% and 82.0%, respectively [HR 1.38 (1.03–1.85)], $P = 0.037$, as shown in Fig. 2a. Other factors shown to be associated with UTIs on univariate analysis were female gender [HR 2.61 (1.91–3.55), $P < 0.0001$], diabetes [HR 1.48 (1.05–2.08), $P = 0.013$], deceased donor transplants [HR 1.52 (1.13–2.02), $P = 0.006$], older age [median age in UTI+ patients was 54.13 (51.56–57.73) and in UTI patients was 51.13 (49.72–52.38), $P = 0.018$] and lower body mass [median weight in UTI patients was 75.0 (73.10–76.22) and in the UTI+ patients was 71.90 (66.90–75.42), $P = 0.034$]. Multivariate analysis of patient-related factors associated with urosepsis revealed that increasing age HR 1.01 (1.00–1.03), $P = 0.032$, female gender HR 2.88 (2.14–3.87), $P < 0.001$ and diabetes HR 1.57 (1.13–2.18), $P = 0.007$ were risk factors, whilst receiving a living donor transplant HR 0.67 (0.49–0.91), $P = 0.01$ and AD alemtuzumab HR 0.63 (0.46–0.86), $P = 0.004$ were protective.

There was no difference in bacteraemia-free survival at 1 year between the SD and AD group at 92.8% and 94.4%, respectively [HR 1.29 (0.76–2.19)], $P = 0.37$, as shown in Fig. 2b. Diabetes was the only risk factor present at the time of transplantation which was found to be associated with the development of bacteraemia [HR 1.87 (1.08–3.23), $P = 0.026$].

Fungal infection-free survival in the first year post-transplant was inferior in the SD group at 97.0% compared with 99.4% in the AD group, HR 2.15 (2.00–13.28) $P = 0.015$, as shown in Fig. 2c. On multivariate analysis of factors present at the time of transplant associated with fungal infection revealed diabetes HR 3.34 (1.33–8.73), $P = 0.010$ was a risk factor, whilst receiving AD alemtuzumab was protective HR 0.19 (0.04–0.84), $P = 0.028$.

There was no difference in CMV-free survival between the groups at 98.3% and 98.2% in the SD and AD groups, respectively, $P = 0.92$; there was no difference in BK-free survival at 97.5% and 98.2% in the SD and AD groups, respectively, $P = 0.52$ or EBV-free survival at 100.0% and 99.4% in the SD and AD groups, respectively, $P = 0.08$.

The results of a further analysis to assess the impact of infection rates on patients less than 75 kg in dose-adjusted alemtuzumab are shown in Appendix S1. Patients less than 75 kg in the AD group received less than 30 mg of alemtuzumab, and compared with patients <75 kg in the SD group, they had a superior

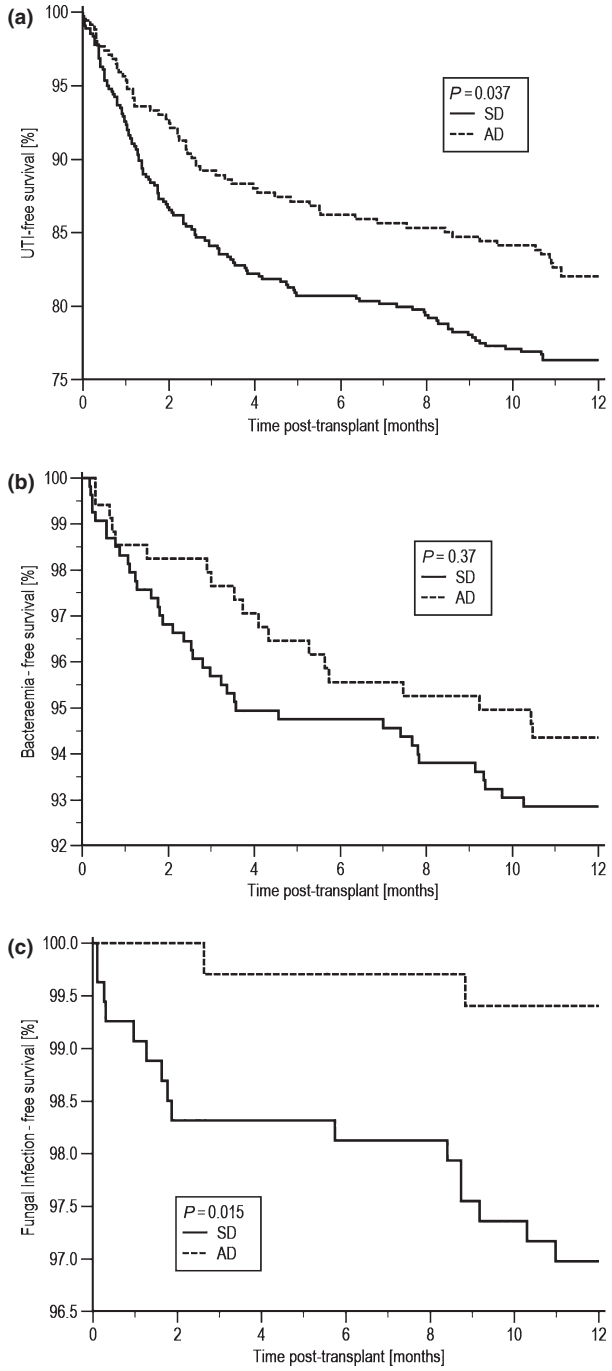

Figure 2 Comparison of the 1-year urosepsis-, bacteraemia- and fungal infection-free survival between the standard dose and adjusted dose (AD) groups. (a) Urosepsis was more common in the SD group compared with the AD group. HR 1.38 (1.03–1.85), $P = 0.037$. (b). There was no difference in the incidence of bacteraemias in the SD group compared with the AD groups, HR 1.29 (0.76–2.19), $P = 0.37$. (c). Fungal infections were more common in the SD group compared with the AD groups, HR 5.15 (2.00–13.28), $P = 0.015$.

infection-free survival in the first year post-transplant, at 70.8% and 60.6%, respectively, $P = 0.018$. Conversely, the overall infection-free survival in the patients >75 kg was no different in patients receiving AD compared with SD alemtuzumab dosing at 65.8% and 66.5%, respectively, $P = 0.84$.

Discussion

In this study, we have shown that compared with a control group of renal transplant recipients who received a standard fixed dose of alemtuzumab, patients who received a dose adjusted for body weight had higher lymphocyte counts and less infection episodes, with no increased risk of rejection in the first year post-transplant. We believe this is the first reported study of the impact of alternative alemtuzumab dosing on patient and transplant outcomes to be reported in solid organ transplantation. Although conclusions are limited by its retrospective nature, it does question the dogma of whether dosing of monoclonal antibodies in transplantation is optimized at an individual level to achieve the most favourable outcomes.

The use of monoclonal antibodies in transplantation is likely to steadily increase over the years to come as the molecular pathogenesis of rejection is unravelled[2]. These agents will have a more targeted approach compared with historic immunosuppression therapies and are likely to be more efficacious. However, given that the aim of the effector mechanisms of the mAbs used in transplantation will involve interference with immune function, infection complications are probably unavoidable. Any mAb used in transplant patients would have been subjected to rigorous safety and regulatory review[16]. However, as is the case for alemtuzumab, the first in human studies and preliminary clinical data is not necessarily performed in patients with the same therapeutic aim or indication[6,17–19]. The aim of alemtuzumab in transplantation was to induce a state of tolerance in the early post-transplant period[20,21]. The frequency and cumulative dosing requirement of alemtuzumab are different for transplantation when compared with either chronic lymphocytic leukaemia or multiple sclerosis, for which it is licensed[19]. Also, when considering the optimal dosing for mAbs in transplantation, the additive effect of maintenance immunosuppression needs to be taken into account when trying to minimize adverse effects. Establishing the correct dosing of any mAb in transplantation which is applicable to all transplant programmes will

be further complicated by the heterogeneity of maintenance immunosuppression used. For example, we saw relatively few viral complications in our study cohort, which may in part reflect the lack of mycophenolate mofetil (MMF) used in our patients [22]. Variation in dosing of transplant induction agents is not unique to alemtuzumab. The PK and PD of ATG were first studied 20 years ago, and still the ideal dose is not known[23]. ATG is dosed according to body weight and the recommended total cumulative doses is wide and ranges from 3 to 13.5 mg/kg[24]. It is known that the dose of ATG is associated with the rate of lymphocyte repletion, and prolonged ATG induced lymphopenia is associated with mortality and morbidity[25]. Studies that have been performed comparing different dosing regimens all report lower infection complications with the lower doses [11–13]. Despite this, there is still no formal consensus or guidance from regulatory bodies on the most favourable dose.

Although alemtuzumab is not licensed for use in transplantation, it has been increasingly used with favourable outcomes when compared with both IL-2 receptor monoclonal antibodies and ATG [3,26–34]. The reported doses of alemtuzumab used in published controlled trials have varied, and a summary of the doses used are shown in Table 3. The rationale for the prescribed doses were not given in these studies with the exception of the 3C collaborative trial, who reported that 30 mg instead of 60 mg was given to patients >60 years to prevent infection[31]. Like most mAbs, alemtuzumab is considered to have a large therapeutic window, which is compatible with fixed dosing [5,8,17,18]. However, whilst a large therapeutic window may be acceptable in terms of a drug's efficacy, it may not be tolerable in terms of its side effect profile at a patient level. The concern with fixed dose prescribing is that there may be risk of over exposure in patients of low weight, and under expose those patients of high weight. In terms of alemtuzumab use in transplantation, this would translate to rejection risk with under dosing and infection risk with overdosing. Although we did not see an increase in rejection rates, we did see overall less infection in the dose-adjusted group. We know from other studies in transplantation that higher doses of alemtuzumab are associated with increased infection rates, with disseminated fungal infections being of particular concern[35–37]. This has been most commonly reported in patients who have received repeated doses to treat rejection episodes[37]. Reassuringly, the recently published 3C study did not report an increased risk of serious infection in the alemtuzumab arm compared with the basiliximab induction arm in the first 6 months post-transplant [31]. In the INTACT study, renal transplant patients receiving alemtuzumab had a higher incidence of infection compared with the basiliximab patients, but a lower incidence of infection compared with the ATG group [30]. This suggests that current rates of infection with alemtuzumab are not excessive when compared with these other commonly used agents. The question which may be posed by our study is that can these infection rates be improved? Given that infection remains one of the major causes of mortality and morbidity post-transplant, one could argue that it should be explored[38].

To date, the PK and PD properties of alemtuzumab have been studied in patients outside of solid organ transplantation[17]. In a study of patients with chronic lymphocytic leukaemia, alemtuzumab clearance was shown to be nonlinear, with rate of elimination dependent upon WCC [17]. No other covariates influenced PK including age, weight and gender[17]. Regarding extrapolation of this finding to renal transplant patients, it has been

Table 3. Alemtuzumab doses reported from controlled trials.

Study	Year	Dosing regime	Dose (mg)
Vathsala, A *et al.* [28]	2005	20 mg iv on day 0 and 1	40
Thomas, PG *et al.* [3]	2007	30 mg iv day 0	30
Ciancio, G *et al.* [35]	2008	0.3 mg/kg on day 1 and 4	0.6 mg/kg
Margreiter, R *et al.* [30]	2008	20 mg iv on day 0 and 1	40
Hanaway, MJ *et al.* [31]	2011	30 mg iv on day 0	30
Lu, TM *et al.* [34]	2011	15 mg iv day 0 and 1	30
Chan, KK *et al.* [33]	2011	30 mg iv day 0	30
Welberry Smith, M *et al.* [27]	2013	30 mg iv day 0	30
The 3C collaborative [32]	2014	30 mg iv* day 0 (and day 1 if <60 years old)	≤60

*Administration via the subcutaneous route was also permitted.

shown that WCC are lower in patients with end stage renal disease (ESRD) compared with healthy controls [11]. Therefore, equivalent therapeutic doses may not be required in patients with ESRD. In fact, much larger fixed doses are given outside of renal transplantation to treat both CLL and multiple sclerosis[19]. Another interesting observation from CLL studies is the direct relationship demonstrated between alemtuzumab concentration and clinical response[17]. In transplantation, alemtuzumab levels are not measured in clinical practice, and we believe there has been no study correlating levels in the early post-transplant period with rejection and infection episodes, which may be an area for future work. Also, the effect of alemtuzumab dose on lymphocyte recovery has been shown in a study in allogeneic hematopoietic cell transplant patients[39]. In that study, it was shown that higher doses of alemtuzumab correlated with a prolongation of recovery of lymphocyte subpopulations[39]. Therefore, with further data which incorporates lymphocyte subpopulations and alemtuzumab levels together with clinical outcome data in renal transplantation, it may be possible to reduce the doses of alemtuzumab. The aim would be to achieve the optimal dose needed to balance the risk of rejection and infection.

To conclude, this study does not offer unequivocal proof that dose adjusting alemtuzumab for weight reduces the risk of infection postrenal transplant. It does, however, highlight the complexity of dosing monoclonal antibodies, with regard to optimizing the specific clinical response required in transplantation. There are likely to be an increasing number of monoclonal antibodies used in transplantation to either help circumvent or treat rejection. Given their impact on immune function, it will be of paramount importance that any mAbs used have their appropriate dosing established for that indication, either in the form of clinical trials or by robust collaborative reporting of outcomes.

Authorship

MW: collected and analysed data and wrote the paper. DG: collected data and reviewed paper. AGM: reviewed the paper. DT: participated by initiating study and reviewing the paper.

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Conflicts of interest

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Appendix S1. Infection free survival in patients in AD and SD groups by weight.

Appendix S2. Comparison of lymphocyte counts in AD and SD patients, according to whether they experienced infection or rejection.

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