Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Effect of interleukin-2 receptor antibody therapy on acute rejection risk and severity, long-term renal function, infection and malignancy-related mortality in renal transplant recipients

Wai Lim,[1,2] Steve Chadban,[2,3] Scott Campbell,[2,4] Hannah Dent,[2,5] Graeme Russ,[2,6] and Stephen McDonald[2,6]

1 Department of Renal Medicine, Sir Charles Gairdner Hospital, Perth, WA, Australia
2 ANZDATA Registry, Adelaide, SA, Australia
3 Renal Unit, Royal Prince Alfred Hospital, Sydney, NSW, Australia
4 Renal Unit, Princess Alexandra Hospital, Brisbane, Qld, Australia
5 Discipline of Public Health, University of Adelaide, Adelaide, SA, Australia
6 Nephrology and Transplantation Services, Royal Adelaide Hospital, Adelaide, SA, Australia

Keywords
induction, interleukin-2 receptor antibody, kidney transplant, rejection.

Correspondence
Dr Wai Lim PhD, Department of Renal Medicine, Sir Charles Gairdner Hospital, Perth, WA 6009, Australia.
Tel.: 08 9346 2799; fax: 08 9346 3942;
e-mail: wai.lim@health.wa.gov.au

Received: 7 March 2010
Revision requested: 1 April 2010
Accepted: 17 May 2010
Published online: 7 June 2010

doi:10.1111/j.1432-2277.2010.01124.x

Summary

In renal transplantation, the use of interleukin-2 receptor antibody (IL-2Ra) has been associated with reduced rejection rates, but the effect of this agent on rejection severity and type, long-term graft function and risk of infection and malignancy-related mortality remains unclear. Using Australia and New Zealand Dialysis and Transplant Registry, all live- and deceased-donor renal transplant recipients in Australia between 2000 and 2006 were included. Of the 3344 renal transplant recipients, 1874 (56.0%) received no induction and 1470 (44.0%) had received IL-2Ra. Compared with no induction, IL-2Ra was associated with reduced rejection risk (relative risk 0.70, 95% CI 0.60, 0.81) and higher estimated glomerular filtration rate at 5 years (difference in means 3.51, 95% CI 0.83, 6.19). Severity and type of rejection were similar in both the groups. The adjusted rate of death attributed to malignancy for no induction and IL-2Ra per 1000 patient-years was 1.48 and 1.63, respectively, whereas death attributed to infection was 2.42 and 2.16 respectively. This registry analysis demonstrates that IL-2Ra induction in kidney transplantation is associated with substantial clinical benefits of reduced risk of acute rejection and improved long-term graft function without an increase in adverse events.

Introduction

Renal transplantation confers a significant survival advantage for patients with end-stage renal disease compared with those remaining on dialysis [1]. Acute rejection, which occurs generally within the first few months post-transplant, remains an important determinant of short- and long-term graft survival [2]. Induction therapy with T-cell depletive antibodies [T-cell Ab; including polyclonal (anti-thymocyte globulin, thymoglobulin, anti-lymphocyte globulin) and monoclonal (OKT3) antibodies] or interleukin (IL)-2 receptor antibodies (IL-2Ra) directed against activated T cells (basiliximab and daclizumab) is designed to reduce acute rejection risk in kidney transplantation. IL-2Ra was introduced in 1997 as an alternative induction agent and because IL-2Ra has no direct effect on nonactivated T cells, these agents are not associated with increased infection risk [3,4]. The effectiveness of IL-2Ra in preventing rejection is similar to T-cell Ab in both paediatric and adult renal transplant recipients

[5–8], but without the increased risk of infection- and malignancy-related morbidity and mortality associated with T-cell Ab [9,10].

In Australia, IL-2Ra is the preferred induction agent with its usage increasing from 9.5% in 2000 to 57.1% in 2006, while the use of T-cell Ab has steadily fallen to 4% in 2006 [11]. Although it is well established that IL-2Ra reduces rejection risk, the effect of IL-2Ra on rejection severity and type, and longer-term graft survival and function has not been extensively evaluated. Thus, the aim of the present study was to determine the efficacy of IL-2Ra compared with no induction on renal graft and patient outcomes including acute rejection (risk, severity and type), glomerular filtration rate (GFR), graft and patient survival, infection and malignancy rates.

Patients and methods

Study population

Using the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry, all live-donor (LD) and deceased-donor (DD) renal transplant recipients in Australia from 2000 to 2006 were included in this study. Multiple-organ graft recipients and recipients aged <16 years at the time of transplant were excluded from the study.

Data collection

Recorded baseline data included donors' characteristics such as age (<50, 50–59 and ≥60 years), gender and source (DD and LD); and recipients' characteristics including age (16–29, 30–49 and ≥50 years), gender, race (indigenous and nonindigenous), body mass index at the time of transplant (BMI; categorized into 0–<18.5, 18.5–<25, 25–<30 and ≥30 kg/m^2), prior grafts, comorbid medical conditions [smoking, cardiovascular disease (CVD) and diabetes mellitus], peak panel reactive antibody (PRA; <10%, 10–25% and >25%), total ischaemic time if DD (DD <12 h, DD 12–18 h and DD >18 h) and time on dialysis (categorized into ≤1 year, >1–3 years on dialysis and >3 years on dialysis). The number of HLA-mismatch(es) was used as a continuous variable in the analysis (i.e. 0–6 HLA-mismatches). Initial immunosuppression at the time of transplant including calcineurin-inhibitor [CNI; categorized as cyclosporine, tacrolimus, CNI with mammalian target of rapamycin (mTOR) inhibitors or none], antimetabolite agents (mycophenolate mofetil, azathioprine or none) and use of corticosteroids were included in the analysis. Individual renal units determined the choice of initial immunosuppressant. The transplant period (categorized into cohorts of 2000–2002, 2003–2004 and 2005–2006) and transplanting states (Western Australia, South Australia, New South Wales, Queensland, Victoria) were included in the analysis. The report of comorbid medical conditions was collected at the commencement of renal replacement therapy.

Clinical outcomes

Clinical outcomes of this study included graft and patient survival [including death-censored graft failure (DCGF) and death with functioning graft (DFG)], estimated GFR (eGFR) calculated by the abbreviated Modification of Diet in Renal Disease formula [12] at 1 and 5 years post-transplant and acute rejection occurring in the first 6 months post-transplant. Only clinical rejection episodes were reported and biopsies were performed at the discretion of individual units. Other outcomes analysed included death attributed to infections or malignancies. For the purpose of this study, outcome data of all patients were censored at December 2007. Potential interactions between the use of IL-2Ra and confounders were examined for all outcomes.

Statistics

Baseline characteristics were expressed as frequency (percentage) for categorical data and comparisons between groups (no induction and IL-2Ra) were made by chi-square test or Fisher's exact test, as appropriate. Acute rejection within 6 months was modelled using log-binomial regression to estimate relative risks (RR). Graft and patient survival were examined using Kaplan–Meier methods and Cox regression to estimate hazard ratios (HR). DCGF and DFG were competing events, and hence were examined by estimating cumulative incidence and performing Cox regression on an augmented dataset and stratifying by event type to estimate cause-specific HR. Linear regression was used to examine eGFR at 1 and 5 years by estimating differences in mean (MD) eGFR. Rates of death attributed to infection and malignancy were adjusted for confounders using Poisson regression and mortality rate ratios were obtained. All point estimates are presented with 95% confidence intervals. The covariates included in the adjusted models were donors' (age, source, gender and cause of death) and recipients' characteristics (including gender, BMI age, peak PRA, diabetes mellitus, CVD, HLA-matching, prior grafts, smoking, time on dialysis, initial type of immunosuppression, total ischaemic time) and transplant states and period. Statistical analysis was performed using STATA/IC 10 (Stata Corporation, College Station, TX, USA). Two-tailed *P*-values of <0.05 were considered statistically significant.

Results

Baseline characteristics

Of the 3344 live- and deceased-donor renal transplant recipients included in this study, 1874 (56.0%) did not receive any induction therapy, whereas 1470 (44.0%) had received IL-2Ra induction therapy. Baseline variables of recipients stratified by the use of induction therapy are shown in Table 1. IL-2Ra was used more frequently in deceased donor grafts, prior grafts and recipients with ≥3 years on dialysis. The use of IL-2Ra increased from 23% during the period of 2000–2002 to 46% during 2003–2004 and to 66% during 2005–2006. Of the highly sensitized recipients, 54% of recipients with prior grafts, 45% of recipients with PRA >25% and 46% of those with ≥3 HLA-mismatches had received IL-2Ra. Of recipients receiving initial cyclosporine or tacrolimus, 38% and 51% had received IL-2Ra compared with 61% and 44% who had received no induction respectively.

Table 1. Baseline characteristics of recipients by use of induction therapy.

Induction therapy	No induction (%)	IL-2Ra (%)
Donor age (years)		
<50	1062 (56.7)	833 (56.7)
50–59	505 (27.0)	380 (25.8)
≥60	307 (16.3)	257 (17.5)
Donor gender*		
Female	821 (43.8)	740 (50.3)
Male	1053 (56.2)	730 (49.7)
Recipient age (years)		
16–29	276 (14.7)	213 (14.5)
30–49	805 (43.0)	623 (42.4)
≥50	793 (42.3)	634 (43.1)
Recipient gender		
Female	686 (36.6)	576 (39.2)
Male	1188 (63.4)	894 (60.8)
Recipient race		
Caucasian	1795 (95.8)	1420 (96.6)
Indigenous	79 (4.2)	50 (3.4)
Recipient body mass index (kg/m^2)		
0–18.5	70 (3.8)	60 (4.1)
>18.5–25	840 (44.9)	640 (43.6)
>25–30	650 (34.8)	511 (34.8)
>30	309 (16.5)	258 (17.5)
Grafts*		
Primary	1811 (96.6)	1369 (93.1)
Prior	63 (3.4)	101 (6.9)
Recipient diabetes		
No	1671 (89.2)	1312 (89.2)
Yes	203 (10.8)	158 (10.8)
Recipient cardiovascular disease		
No	1616 (86.2)	1284 (87.3)
Yes	258 (13.8)	186 (12.7)
Recipient smoking history		
Nonsmoker	1067 (57.0)	869 (59.1)
Current smoker	231 (12.3)	151 (10.3)
Ex-smoker	575 (30.7)	450 (30.6)
Recipient HLA-mismatches*		
0	188 (10.0)	66 (4.5)
1–2	607 (32.5)	447 (30.5)
3–4	734 (39.3)	567 (38.7)
5–6	340 (18.2)	384 (26.3)
Recipient time on dialysis (years)*		
0–1	523 (27.9)	458 (31.2)
>1–3	670 (35.8)	469 (31.9)
>3	681 (36.3)	543 (36.9)
Recipient peak PRA*		
0–<10%	1349 (72.1)	1044 (71.1)
10–25%	246 (13.1)	149 (10.2)
>25%	278 (14.8)	275 (18.7)
Donor source/cold ischaemia time*		
Live-donor	698 (37.7)	688 (47.0)
Deceased donor <12 h	360 (19.4)	219 (15.0)
Deceased donor 12–18 h	566 (30.6)	416 (28.4)
Deceased donor >18 h	228 (12.3)	140 (9.6)

Acute rejection

Within the first 6 months after transplant, episodes of acute rejection occurred in 35% and 21% of recipients with no induction therapy and IL-2Ra respectively (Table 2). The use of IL-2Ra was associated with a significant reduction in risk of acute rejection at 6 months compared with no induction (Table 3). Among recipients who had received initial cyclosporine, 35% and 20% of recipients who had received no induction or had been given IL-2Ra, respectively, had experienced acute rejection ($P < 0.001$). Among recipients who had received initial tacrolimus, 32% and 23% of recipients who had no induction or had been given IL-2Ra, respectively, had experienced acute rejection ($P = 0.003$). Other donor and recipient characteristics, which were independently predictive of increased acute rejection, include older donors, female donors, younger recipients, Caucasian race, overweight/obese (BMI ≥ 25 kg/m^2) recipients, current smoker, prior grafts, increasing number of HLA-mismatches, PRA >25% and transplant prior to 2003. The effect of HLA-mismatches on acute rejection is linear, that is, for each additional HLA-mismatch, there is an increased RR of acute rejection of 16% (RR 1.16, 95% CI 1.11, 1.20). There was no interaction between induction therapy and other covariates with respect to rejection.

In those recipients who had experienced rejection, we next sought to determine the effect of IL-2Ra on multiple rejection episodes and vascular rejection. Of recipients who had experienced rejection, 29% and 28% of recipients who did not receive induction and IL-2Ra, respectively, had experienced ≥2 rejection episodes ($P = 0.05$). After adjustment for confounders, there was no

Table 1. (Continued)

Induction therapy	No induction (%)	IL-2Ra (%)
Recipient initial CNI*		
None	57 (3.1)	64 (4.4)
Cyclosporine	1256 (67.1)	787 (53.7)
Tacrolimus	461 (24.6)	537 (36.6)
CNI + TOR inhibitors	97 (5.2)	79 (5.3)
Recipient initial antimetabolite*		
None	197 (10.5)	98 (6.7)
Mycophenolate	1606 (85.8)	1326 (90.2)
Azathioprine	69 (3.7)	46 (3.1)
Corticosteroids at transplant*		
No	80 (4.3)	71 (4.8)
Yes	1794 (95.7)	1399 (95.2)
Transplant period*		
2000–2002	1062 (56.7)	326 (22.2)
2003–2004	504 (26.9)	456 (31.0)
2005–2006	308 (16.4)	688 (46.8)
Transplanting state*		
New South Wales	537 (28.7)	447 (30.4)
Victoria	586 (31.3)	281 (19.1)
Queensland	192 (10.2)	455 (31.0)
South Australia	317 (16.9)	156 (10.6)
Western Australia	242 (12.9)	131 (8.9)

PRA, peak panel reactive antibody; IR-2Ra, interleukin-2 receptor antibody; CNI, calcineurin-inhibitor.
*Chi-square $P < 0.05$, data expressed as number (%).

Table 2. Transplant outcomes by induction therapy.

Outcome	No induction *n* = 1874	IL-2Ra *n* = 1470
Acute rejection	650 (34.7%)	295 (20.1%)
Overall graft failure		
1 year	6.8 (5.7–8.1)	5.9 (4.8–7.3)
5 years	15.5 (13.8–17.4)	16.5 (14.2–19.2)
DCGF		
1 year	4.6 (3.7–5.6)	4.1 (3.2–5.2)
5 years	8.7 (7.4–10.1)	10.1 (8.2–12.1)
DFG		
1 year	2.2 (1.6–3.0)	1.8 (1.2–2.6)
5 years	6.8 (5.6–8.1)	6.5 (5.0–8.2)
Death		
1 year	3.1 (2.4–4.0)	2.5 (1.8–3.5)
5 years	8.8 (7.5–10.3)	8.4 (6.7–10.6)
eGFR		
1 year	51.97 ± 17.24 (*n* = 1737)	52.82 ± 17.58 (*n* = 1374)
5 years	50.23 ± 18.78 (*n* = 885)	52.48 ± 20.06 (*n* = 263)

Data are expressed as number (%) for acute rejection within 6 months and mean ± SD for eGFR. Kaplan–Meier failure estimates (%) with 95% confidence intervals are presented by overall graft failure and death. Cumulative incidence estimates (%) with 95% confidence intervals are presented for DCGF and DFG.
DCGF, death-censored graft failure; DFG, death with functioning graft; eGFR, estimated glomerular filtration rate.

significant difference between IL-2Ra and no induction (RR 1.02, 95% CI 0.78, 1.35; $P = 0.87$).

Eleven per cent and 13% of recipients who had no induction and IL-2Ra, respectively, had experienced biopsy-proven vascular rejection ($P = 0.75$). In the adjusted model, there was no association between the use of induction therapy and the risk of vascular rejection (IL-2Ra – RR 1.14, 95% CI 0.70, 1.84; $P = 0.60$). In addition, there was no association between the use of IL-2Ra and the severity of rejection (data not shown).

Overall graft failure

Kaplan–Meier survival estimates of overall graft survival were 92% and 82% in recipients without induction therapy, and 94% and 82% in recipients who had received IL-2Ra, at 1 and 5 years respectively. (Table 2). There was no significant association between the use of induction therapy and overall graft failure in the Cox regression model used to adjust for confounders (Table 4). For overall graft failure, recipients initiated on either cyclosporine or tacrolimus had similar graft survival with and without IL-2Ra. The 1-, 3- and 5-year graft survival of recipients initiated on cyclosporine and who had no induction was 91%, 85% and 80%, respectively, compared to 94%, 86% and 81%, respectively, in recipients who had received IL-2Ra. The 1-, 3- and 5-year graft survival of recipients initiated on tacrolimus and who had no induction was 92%, 90% and 84%, respectively, compared to 93%, 88% and 82%, respectively, in recipients who had received IL-2Ra. Donor and recipient characteristics associated with increased risk of overall graft failure include older donors, indigenous race, diabetes, current smokers, CVD, deceased donor grafts, 3 or more years on dialysis and transplant prior to 2003. There was no interaction between the use of induction therapy and covariates with respect to overall graft failure.

Death-censored graft failure

Cumulative incidence estimates of DCGF were 5% and 9% in recipients with no induction therapy, and 4% and 10% in recipients who received IL-2Ra (Table 2), at 1 and 5 years respectively. Donor and recipient characteristics associated with higher risk of DCGF include older donors, younger recipients, indigenous race, prior grafts, current smoker and deceased donor grafts. There was no interaction between the use of induction therapy and covariates with respect to DCGF.

Death with functioning graft

Cumulative incidence estimates of DFG at 1 and 5 years were 2% and 7% in recipients with no induction therapy,

Table 3. Multivariate analysis of induction therapy and acute rejection (log-binomial regression) and eGFR at 1 and 5 years (linear regression).

	Acute rejection	eGFR 1 year	eGFR 5 years
Induction			
None	1.00	0.00	0.00
IL-2Ra	0.70 (0.60, 0.81)*	0.87 (−0.45, 2.19)	3.51 (0.83, 6.19)*
Donor age			
<50	1.00	0.00	0.00
50–59	1.29 (1.13, 1.48)*	−8.63 (−9.96, −7.30)*	−8.27 (−10.70, −5.84)*
≥60	1.41 (1.21, 1.65)*	−15.02 (−16.59, −13.46)*	−14.75 (−18.05, −11.45)*
Donor gender*			
Female	1.00	0.00	0.00
Male	0.85 (0.76, 0.96)*	4.23 (3.11, 5.35)*	4.55 (2.44, 6.66)*
Recipient age			
16–29	1.00	0.00	0.00
30–49	0.87 (0.74, 1.02)	−5.86 (−7.57, −4.15)*	0.78 (−3.82, 2.26)
≥50	0.71 (0.59, 0.85)*	−5.49 (−7.31, −3.68)*	−0.22 (−3.52, 3.07)
Recipient BMI (kg/m^2)			
0–18.5	0.86 (0.61, 1.19)	9.76 (6.75, 12.76)*	0.75 (−5.25, 6.76)
>18.5–25	1.00	0.00	0.00
>25–30	1.15 (1.01, 1.31)*	−1.49 (−2.75, −0.22)*	−2.38 (−4.75, 0.00)
>30	1.20 (1.01, 1.41)*	−4.26 (−5.87, −2.66)*	−5.15 (−8.20, −2.09)*
Recipient cardiovascular disease			
No	1.00	1.00	1.00
Yes	0.98 (0.81, 1,19)	1.87 (0.07, 3.66)*	2.30 (−1.18, 5.78),
Recipient smoking			
Nonsmoker	1.00	0.00	0.00
Current smoker	1.21 (1.02, 1.44)*	−1.56 (−3.41, 0.28)	−2.79 (−6.32, 0.73)
Ex-smoker	1.07 (0.94, 1.23)	−1.89 (−3.17, −0.61)*	−3.49 (−5.86, −1.12)*
Grafts			
Primary	1.00	0.00	0.00
Prior	1.29 (1.00, 1.65)*	−0.49 (−3.20, 2.26)	−1.83 (−7.97, 4.31)
Donor source			
Live donor	1.00	0.00	0.00
Deceased <12 h	0.86 (0.71, 1.04)	0.59 (−1.16, 2.34)	2.98 (−0.37, 6.33)
Deceased donor 12–18 h	0.91 (0.77, 1.07)	−1.34 (−2.88, 0.21)	0.16 (−2.75, 3.07)
Deceased donor >18 h	0.88 (0.71, 1.08)	−3.84 (−5.88, −1.80)*	0.23 (−3.35, 3.81)
HLA-mismatches	1.16 (1.11, 1.20)*	−0.15 (−0.51, 0.21)	−0.27 (−0.97, 0.43)
Recipient peak PRA			
0–<10%	1.00	0.00	0.00
10–25%	0.91 (0.74, 1.11)	−0.36 (−2.18, 1.46)	1.72 (−1.66, 5.10)
>25%	1.32 (1.12, 1.54)*	−2.46 (−4.13, −0.78)*	−3.64 (−6.86, −0.42)*
Antimetabolite			
None	1.00	0.00	0.00
Mycophenolate	1.01 (0.74, 1.40)	4.12 (1.10, 7.14)*	5.26 (−0.86, 11.39)
Azathioprine	1.17 (0.75, 1.82)	5.97 (1.66, 10.29)*	9.11 (1.19, 17.04)*
Corticosteroids			
No	1.00	1.00	1.00
Yes	0.74 (0.58, 0.95)*	−3.54 (−6.34, −0.73)*	−6.99 (−12.13, −1.85)*
Transplant period			
2000–2002	1.00	0.00	–
2003–2004	0.88 (0.77, 1.02)	0.21 (−1.21, 1.63)	–
2005–2006	0.76 (0.65, 0.89)*	1.09 (−0.43, 2.61)	–

*$P < 0.05$, data expressed as relative risk for rejection or as difference in mean values for eGFR with 95% confidence interval. Only significant variables are shown in this table, but models also included recipient gender, indigenous race, diabetes, duration on dialysis, initial CNI and transplanting state.

eGFR, estimated glomerular filtration rate; PRA, panel reactive antibody; CNI, calcineurin-inhibitor.

Table 4. Multivariate analysis of induction therapy and graft and patient survival.

	Overall graft failure	DCGF	DFG	Patient death
Induction				
None	1.00	–	1.00	1.00
IL-2Ra	1.23 (0.99, 1.53)	–	1.08 (0.76, 1.52)	1.01 (0.74, 1.39)
Donor age				
<50	1.00	1.00	1.00	1.00
50–59	1.37 (1.10, 1.70)*	1.75 (1.32, 2.31)*	0.95 (0.66, 1.35)	1.00 (0.73, 1.36)
≥60	1.84 (1.46, 2.33)*	2.36 (1.75, 3.18)*	1.24 (0.84, 1.82)	1.10 (0.78, 1.55)
Recipient age				
16–29	1.00	1.00	1.00	1.00
30–49	0.76 (0.56, 1.02)	0.64 (0.46, 0.90)*	1.34 (0.69, 2.61)	1.69 (0.90, 3.16)
≥50	1.00 (0.74, 1.35)	0.57 (0.39, 0.81)*	3.11 (1.63, 5.95)*	3.57 (1.93, 6.61)*
Recipient race				
Nonindigenous	1.00	1.00	1.00	1.00
Indigenous	2.12 (1.49, 3.01)*	2.42 (1.52, 3.83)*	1.77 (1.02, 3.06)*	2.07 (1.30, 3.32)*
Recipient diabetes				
No	1.00	1.00	1.00	1.00
Yes	1.43 (1.10, 1.87)*	1.16 (0.79, 1.71)	1.80 (1.24, 2.63)*	1.81 (1.30, 2.53)*
Recipient CVD				
No	1.00	1.00	1.00	1.00
Yes	1.71 (1.35, 2.17)*	1.35 (0.96, 1.90)	2.22 (1.59, 3.10)*	1.95 (1.44, 2.64)*
Recipient smoking				
Nonsmoker	1.00	1.00	1.00	1.00
Current smoker	1.50 (1.15, 1.95)*	1.66 (1.19, 2.33)*	1.20 (0.78, 1.87)	1.20 (0.82, 1.77)
Ex-smoker	1.17 (0.95, 1.45)	1.25 (0.95, 1.65)	1.07 (0.78, 1.49)	1.03 (0.77, 1.37)
Grafts				
Primary	1.00	1.00	1.00	–
Prior	1.37 (0.93, 2.01)	1.73 (1.11, 2.69)*	0.57 (0.23, 1.43)	–
Donor source				
Live donor	1.00	1.00	1.00	1.00
DD <12 h	1.46 (1.09, 1.96)*	1.52 (1.03, 2.24)*	1.45 (0.92, 2.29)	1.49 (0.99, 2.24)
DD 12–18 h	1.48 (1.14, 1.92)*	1.81 (1.30, 2.54)*	1.13 (0.74, 1.72)	1.24 (0.85, 1.80)
DD >18 h	1.79 (1.32, 2.44)*	1.86 (1.24, 2.80)*	1.62 (1.01, 2.60)*	1.42 (0.92, 2.20)
Time on dialysis				
0–1 year	1.00	1.00	1.00	1.00
>1–3 years	1.20 (0.90, 1.60)	1.28 (0.89, 1.85)	1.05 (0.66, 1.66)	1.24 (0.81, 1.89)
≥3 years	1.43 (1.05, 1.95)*	1.26 (0.84, 1.88)	1.69 (1.03, 2.76)*	1.81 (1.15, 2.84)*
Recipient initial CNI				
None	1.00	1.00	1.00	1.00
Cyclosporine	0.55 (0.36, 0.83)*	0.41 (0.25, 0.67)*	0.83 (0.39, 1.77)	0.98 (0.49, 1.97)
Tacrolimus	0.58 (0.37, 0.89)*	0.42 (0.26, 0.70)*	0.93 (0.42, 2.06)	1.07 (0.52, 2.22)
CNI + TOR inhibitors	0.35 (0.17, 0.70)*	0.21 (0.09, 0.50)*	0.85 (0.24, 3.02)	1.62 (0.48, 5.43)
Transplant period				
2000–2002	1.00	–	1.00	1.00
2003–2004	0.90 (0.72, 1.13)	–	0.89 (0.63, 1.27)	1.02 (0.74, 1.40)
2005–2006	0.66 (0.49, 0.90)*	–	0.60 (0.36, 1.00)*	0.74 (0.48, 1.14)

*$P < 0.05$, data expressed as hazard ratio with 95% confidence interval. Only significant variables are shown in this table, but models also included donor gender, recipient gender, recipient BMI, number of HLA mismatches, peak PRA, initial antimetabolite, corticosteroid use and transplanting state.

DCGF, death-censored graft failure; DFG, death with functioning graft; IL-2Ra, interleukin-2 receptor antibody; CVD, cardiovascular disease; CNI, calcineurin-inhibitor; PRA, panel reactive antibody.

and 2% and 6% in recipients who received IL-2Ra (Table 2). There was no significant association between induction therapy and DFG in the competing risk Cox regression model (Table 4). Donor and recipient characteristics associated with increased risk of DFG include older recipients, indigenous race, diabetes, CVD, deceased donor grafts with cold ischaemic time ≥18 h and longer duration on dialysis. There was no interaction between

the use of induction therapies and covariates with respect to DFG.

Patient survival

Kaplan–Meier survival estimates of patient and survival were 97% and 91% in recipients without induction therapy, and 98% and 92% in recipients who had received IL-2Ra (Table 2), at 1 and 5 years respectively. There was no association between induction therapy and death (Table 4). Donor and recipient characteristics associated with increased patient death include older recipients, indigenous race, underweight (BMI ≤ 18.5 kg/m^2) recipients, diabetes, CVD and longer duration of dialysis. There was no interaction between induction therapy and covariates with respect to patient survival.

Infection and malignancy

During the study period, 256 (7.8%) patients died, of which 72 (2.2%) deaths were attributed to infection – 48 (2.7%) received no induction therapy and 23 (1.7%) received IL-2Ra. Moreover, of 43 (1.3%) deaths that were attributed to malignancy, 27 (1.5%) and 15 (1.1%) occurred in recipients who received no induction and IL-2Ra respectively. The unadjusted and adjusted rates per 1000 patient-years are shown in Table 5.

Compared with recipients who had not received induction therapy, there was no association between IL-2Ra induction and time to first post-transplant malignancy (Table 5).

Table 5. Induction therapy and infection and malignancies.

	No induction	IL-2Ra
Death from infection†		
Unadjusted rate	5.50 (4.15, 7.30)	5.19 (3.45, 7.81)
Adjusted rate	2.42 (1.46, 4.02)	2.16 (1.22, 3.82)
Death from malignancy†		
Unadjusted rate	3.10 (2.12, 4.51)	3.39 (2.04, 5.62)
Adjusted rate	1.48 (0.78, 2.82)	1.63 (0.80, 3.31)
Time to first post-transplant malignancy	1.00	0.80 (0.61, 1.04)
Time to first nonskin malignancy/melanoma	1.00	1.29 (0.84, 1.98)
Time to first skin malignancy	1.00	0.63 (0.46, 0.88)*

*$P < 0.05$, data expressed as rate per 1000 patient-years (†) or as adjusted hazard ratio with 95% confidence intervals; adjusted for donor age, donor gender, recipient age, recipient gender, recipient BMI, diabetes, CVD, smoking, number of HLA mismatches, peak PRA, donor source by cold ischaemia time, duration on dialysis, initial CNI, antimetabolite and corticosteroid use, year of transplant and transplanting state.

CNI, calcineurin-inhibitor; CVD, cardiovascular disease; PRA, panel reactive antibody; IL-2Ra, interleukin-2 receptor antibody.

Estimated GFR at 1 and 5 years

Compared with no induction therapy, recipients who had received IL-2Ra had similar eGFR at 1 and 5 years (only 40% recipients had reported eGFR at 5 years; Table 2). Using linear regression to adjust for confounders (Table 3), IL-2Ra was associated with higher eGFR at 5 years compared with no induction (MD 3.51, 95% CI 0.83, 6.19; $P = 0.01$) but not at 1 year. Donor and recipient characteristics consistently associated with lower eGFR at 1 and 5 years include older donors, female donors, older recipients, overweight/obese (BMI ≥ 18.5 kg/m^2) recipients, peak PRA >25% and the use of corticosteroids. Deceased donor grafts with a cold ischaemic time ≥18 h were also associated with reduced eGFR at 1 year. There was no interaction between induction therapy and covariates with respect to eGFR.

Discussion

In this registry study, the use of IL-2Ra induction was associated with a reduction in rejection risk and improved long-term graft function compared with no induction, independent of HLA-matching. The reduction in rejection risk with the use of IL-2Ra was observed in recipients initiated on either cyclosporine or tacrolimus, although the benefit appeared greater in those receiving initial cyclosporine. However, despite the reduction in rejection, IL-2Ra was not associated with reduced overall graft failure, including DCGF and DFG up to 8 years post-transplant. In contrast, analysis of other large registry databases including the Organ Procurement and Transplant Network (OPTN; $n = 19\,137$ with 23% IL-2Ra and 39% no induction between 2001 and 2005) and Collaborative Transplant Study (CTS; $n = 112\,122$ deceased-donor transplant recipients with 6% IL-2Ra and 83% no induction between 1985 and 2004) has demonstrated that IL-2Ra induction was associated with reduced risk of rejection and improved graft survival [13–15]. Review of the registry data from OPTN verified that the adjusted RR of triple endpoints of rejection, graft failure and death at 6 months was lower in recipients maintained on tacrolimus, mycophenolate and corticosteroids receiving basiliximab induction compared with no induction (adjusted OR 0.82, 95% CI 0.74, 0.92). Similarly, a recent meta-analysis by Webster *et al.* [16] indicated that the use of IL-2Ra was associated with a 25% reduction in early graft loss, including DFG. However, the association between IL-2Ra and improvement and graft and patient survival remains inconsistent [17,18]. Although the

occurrence of rejection has been associated with an increased risk of early and late graft loss, McDonald *et al.* [2] demonstrated using ANZDATA registry data that recipients with a single episode of cellular rejection were not associated with increased graft loss, whereas the occurrence of multiple rejection or vascular rejection was associated with increased graft loss compared with recipients without rejection. In this study, we had shown that the severity of rejection and the risk of multiple rejection episodes or vascular rejection were similar between recipients receiving IL-2Ra and no induction, which may in part explain the lack of association between IL-2Ra and graft failure in this study.

Previous studies have demonstrated that IL-2Ra induction was associated with significantly better short-term renal function up to 12 months compared with no induction, but this association remains inconsistent [5,19]. In this study, IL-2Ra induction was associated with significantly better long-term renal function at 5 years compared with recipients receiving no induction, presumably related to lower rejection rates, which has been shown to adversely affect renal function post-transplant [2]. As calcineurin-inhibitors have been demonstrated to cause significant nephrotoxicity and chronic kidney damage, it is plausible that in recipients with lower rates of acute rejection, the concurrent reduction in the intensity of immunosuppression, especially of calcineurin inhibitor, may have partly accounted for the superior eGFR at 5 years in recipients receiving IL-2Ra [20]. However, this assumption cannot be accurately explored using registry data.

Although most clinical studies have shown that IL-2Ra has an excellent safety and tolerability with a demonstrable side-effect profile similar to placebo [21], there have been studies suggesting that IL-2Ra may be associated with a 64% reduction in early malignancy at 6 months, possibly related to reduction in immunosuppression [16]. In our study, recipients receiving IL-2Ra had similar risk profile for death attributed to infection or malignancy, although the use of IL-2Ra may be associated with a slower time to first skin malignancy. Given the low event rate of infection and malignancy-related deaths in both IL-2Ra and no induction groups, there may have been a low chance to detect statistical differences between the two groups.

As with all registry analyses involving observations related to retrospective data, there may be unmeasured or residual confounders that could have affected our results. Although this study does not provide direct confirmation concerning the advantage of IL-2Ra induction and transplant outcomes in renal transplant recipients, it does provide powerful data for examining transplant outcomes associated with induction therapy in a large number of observations, which is not restricted to selected group of recipients participating in clinical trials. Although registry analysis cannot replace the results of randomized trials, the recent study by Willoughby *et al.* [14] suggested that a minimum of 1600 recipients would be required per group to detect differences in transplant outcomes between different induction agents in a superiority trial. The restriction of analysis to the transplant period between 2000 and 2006 introduces a potential selection bias, whereby the recipients who did not receive IL-2Ra induction did not for a reason, which might have confounded the comparison. Prior to 2000, IL-2Ra was used in <5% of renal transplant recipients and the inclusion of these historical controls for analysis would be confounded by differences over time, rather than the effect of induction therapy. Confounding by indication for IL-2Ra use, centre-specific protocols or preferences, preferences of immunosuppressant or availability of specific induction agent may be other factors contributing to the differences in outcomes but these factors are not available in registry data.

In this registry analysis, IL-2Ra induction in kidney transplantation was associated with significantly better clinical outcomes of reduced risk of acute rejection and improved long-term graft function without an increased risk of adverse events.

Authorship

WL: designed the research/study, analysed data and wrote paper. HD: analysed data and wrote paper. SC, SC, GR and SM: wrote paper.

Acknowledgements

The authors would like to gratefully acknowledge the substantial contributions of the entire Australian and New Zealand nephrology community (physicians, surgeons, database managers, nurses, renal operators and patients) that provide information to, and maintain, the ANZDATA Registry database. The data reported here have been supplied by the Australia and New Zealand Dialysis and Transplant Registry. The interpretation and reporting of these data are the responsibility of the Editors and in no way should be seen as an official policy or interpretation of the Australia and New Zealand Dialysis and Transplant Registry.

References

1. Wolfe R, Ashby V, Milford E, *et al.* Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999; **341**: 1725.

2. Mcdonald S, Russ G, Campbell S, Chadban S. Kidney transplant rejection in Australia and New Zealand: relationships between rejection and graft outcome. *Am J Transplant* 2007; **7**: 1201.
3. Sandrini S. Use of IL-2 receptor antagonists to reduce delayed graft function following renal transplantation: a review. *Clin Transplant* 2005; **19**: 705.
4. Mattei M, Redonnet M, Gandjbakhch I, *et al.* Lower risk of infectious deaths in cardiac transplant patients receiving basiliximab versus anti-thymocyte globulin as induction therapy. *J Heart Lung Transplant* 2007; **26**: 693.
5. Baron P, Ojogho O, Yorgin P, *et al.* Comparison of outcomes with low-dose anti-thymocyte globulin, basiliximab or no induction therapy in pediatric kidney transplant recipients: a retrospective study. *Pediatr Transplant* 2008; **12**: 32.
6. Sollinger H, Kaplan B, Pescovitz M, *et al.* Basiliximab versus antithymocyte globulin for prevention of acute renal allograft rejection. *Transplantation* 2001; **72**: 1915.
7. Kyllönen L, Eklund B, Pesonen E, Salmela K. Single bolus antithymocyte globulin versus basiliximab induction in kidney transplantation with cyclosporine triple immunosuppression: efficacy and safety. *Transplantation* 2007; **84**: 75.
8. Lebranchu Y, Bridoux F, Büchler M, *et al.* Immunoprophylaxis with basiliximab compared with antithymocyte globulin in renal transplant patients receiving MMF-containing triple therapy. *Am J Transplant* 2002; **2**: 48.
9. Caillard S, Dharnidharka V, Agodoa L, Bohen E, Abbott K. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. *Transplantation* 2005; **80**: 1233.
10. Andres A. Cancer incidence after immunosuppressive treatment following kidney transplantation. *Crit Rev Oncol Hematol* 2005; **56**: 71.
11. Chang S, Russ G, Chadban S, Campbell S, Mcdonald S. Trends in adult post-kidney transplant immunosuppressive use in Australia, 1991–2005. *Nephrology (Carlton)* 2008; **13**: 171.
12. Levey A, Bosch J, Lewis J, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; **130**: 461.
13. Opelz G, Naujokat C, Daniel V, Terness P, Döhler B. Disassociation between risk of graft loss and risk of non-Hodgkin lymphoma with induction agents in renal transplant recipients. *Transplantation* 2006; **81**: 1227.
14. Willoughby L, Schnitzler M, Brennan D, *et al.* Early outcomes of thymoglobulin and basiliximab induction in kidney transplantation: application of statistical approaches to reduce bias in observational comparisons. *Transplantation* 2009; **87**: 1520.
15. Patlolla V, Zhong X, Reed G, Mandelbrot D. Efficacy of anti-IL-2 receptor antibodies compared to no induction and to antilymphocyte antibodies in renal transplantation. *Am J Transplant* 2007; **7**: 1832.
16. Webster A, Ruster L, Mcgee R, *et al.* Interleukin 2 receptor antagonists for kidney transplant recipients. *Cochrane Database Syst Rev* 2010; **1**: CD003897.
17. Nashan B. Antibody induction therapy in renal transplant patients receiving calcineurin-inhibitor immunosuppressive regimens: a comparative review. *BioDrugs* 2005; **19**: 39.
18. Brennan D, Daller J, Lake K, Cibrik D, Del Castillo DTISG. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 2006; **355**: 1967.
19. Ciancio G, Burke G, Gaynor J, *et al.* A randomized trial of three renal transplant induction antibodies: early comparison of tacrolimus, mycophenolate mofetil, and steroid dosing, and newer immune-monitoring. *Transplantation* 2005; **80**: 457.
20. Flechner S, Kobashigawa J, Klintmalm G. Calcineurin inhibitor-sparing regimens in solid organ transplantation: focus on improving renal function and nephrotoxicity. *Clin Transplant* 2008; **22**: 1.
21. Nashan B, Moore R, Amlot P, Schmidt A, Abeywickrama K, Soulillou J. Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. CHIB 201 International Study Group. *Lancet* 1997; **350**: 1193.

