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Does the risk of acute rejection really decrease with increasing recipient age?

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Abstract In corneal transplants the risks of acute rejection and graft failure decrease with increasing recipient age, but kidney graft survival analyses tend to show the opposite effect. Why is this? Cadaveric kidney transplants performed in the UK and Republic of Ireland between 1985 and 1993 (UKTSSA database) were analysed by multifactorial methods to identify major factors affecting graft survival. In a study database that had been censured for technical failure and death with a functioning transplant, it was shown that increasing recipient age was associated with decreasing risk of graft failure at 1 year. This is consistent with the view that kidney transplants, like corneal transplants, are less likely to be acutely rejected as the age of the recipient increases.

Key words Acute-rejection · Renal transplants · Recipient age · Immunosuppression

Introduction

We showed that acute rejection and graft survival in corneal transplants decreased with increasing recipient age from 0 to 80 years suggesting systemic changes due to immuno-senescence favoured graft survival [12]. Paradoxically, in kidney transplants overall graft survival was shown to decrease with increasing recipient age [1]. This may have been due to the fact that recipient death and technical failure of the graft were included as 'graft failure' thereby confounding the analysis [4, 7, 11]. It is well established that the causes of graft failure change with increasing recipient age; 'non-immunological failure' including death tends to increase whilst failure due to acute rejection tends to decrease [2–5, 7, 9, 10]. With a view to exploring the UK database further to see if this apparent paradox could be resolved, we reanalysed the database after technical failures and 'death with a functioning transplant' had been censured.

Materials and methods

A retrospective analysis was conducted on 7250 first cadaveric transplants performed between 1985 and 1993 in 27 centres in the UK and Republic of Ireland. The accuracy of graft failure as a surrogate for acute rejection was improved by censuring failures within the first 7 days and after the 1st year. Cases of 'death with a functioning transplant' were censured from the analysis for similar reasons. Analysis focused on graft failure between 7 and 365 days.

Graft failure is influenced by multiple factors and the independent risk associated with each can be evaluated using Cox's proportional hazards regression model. The influence of a particular factor on probability of graft failure at 12 months is expressed as a 'relative risk' (RR ± 95% confidence interval) [3]. Each factor is stratified into two or more levels and one level chosen as a baseline and assigned an RR of 1.00.

Results

Table 1 gives RRs associated with major factors affecting graft survival. The RR of graft failure within each recipient age band relative to a baseline of 50–59 years declines with increasing age until 50–59 years, but increases thereafter. We concluded that the renal transplant results are consistent with the notion that increasing recip-

Table 1 Multifactorial analysis of first cadaveric kidney transplants in the UK and Republic of Ireland performed between 1985 and 1993. Outcome measure: relative risk of graft failure between 8 and 365 days posttransplant. (*RR* Relative risk, *95% CI* 95% confidence interval of RR, *P value* probability of RR differing from baseline 1.00 by chance)

Factor	Level (baseline)	RR	95% CI	*P* value
Year of transplant	(1985–1987)	(1.00)		
	1988–1990	0.73	0.58–0.91	0.01
	1991–1993	0.63	0.54–0.86	< 0.00
Sex match	(other)	(1.00)		
	female to male	0.78	0.63–0.97	0.03
Donor age (years)	0–18	1.28	0.99–1.67	0.07
	(19–20)	(1.00)		
	56 +	1.86	1.48–2.33	< 0.00
Donor cause of death	(Trauma)	(1.00)		
	Non-trauma	1.43	1.16–1.87	< 0.00
Donor kidney	(Left)	(1.00)		
	Right	0.92	0.76–1.11	0.39
HLA matching	(Beneficial)	(1.00)		
	Non-beneficial	1.44	1.11–1.87	0.01
Shipping	(Local)	(1.00)		
	Exported	1.17	0.94–1.45	0.16
Recipient age at transplant (years)	0–9	2.32	1.27–4.25	0.01
	10–19	1.33	0.90–1.98	0.15
	20–29	1.42	1.06–1.90	0.03
	30–39	1.22	0.91–1.64	0.19
	40–49	1.08	0.81–1.42	0.61
	(50–59)	(1.00)		
	60 +	1.40	1.02–1.92	0.04

ient age is associated with a significant decrease in the probability of developing acute rejection within the 1st year after transplantation.

Discussion

Age-associated decline in acute rejection in kidney transplantation is often obscured by inappropriate statistical analyses that fail to differentiate between the various causes of graft failure. The prevailing clinical experience is that transplantation in the elderly is associated with an increase in life-threatening complications such as cardiovascular disease, infections and cancer. Pharmacokinetic studies reveal little change in immunosuppressive drug metabolism and bioavailability with increasing age [8]. But, many complications in older recipients might be avoided by more modest immunosuppressive therapy. We have shown in pilot studies that there is a dramatic change in the efficacy of calcineurin inhibitors with age as measured in an in vitro model of acute rejection, exemplified elsewhere [6]. Several mechanisms might explain the weakening of acute rejection with increasing age, including increased sensitivity to immunosuppression. An insight into these could lead to improved transplant protocols.

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References

1. Belger MA (1997) Changing donor pattern study of cadaveric kidney donors in the UK and Republic of Ireland. Transplant Proc 29: 106–109
2. Cecka JM, Terasaki PI (1995) Optimal use for older donor kidneys: older recipients. Transplant Proc 27: 801–802
3. Gilks WR, Gore SM, Bradley BA (1986) Analysing transplant survival data. Transplantation 42: 46–49
4. Gjertson DW (1998) The role of death in kidney graft failure. In: Cecka JM, Terasaki PI (eds) Clinical transplants 1998. UCLA Tissue Typing Laboratory, Los Angeles, pp 399–411
5. Gjertson DW, Terasaki PI, Cecka JM, Takemoto S, Cho YW (1997) Senior citizens pool for aged kidneys. Transplant Proc 29: 129
6. Haque KMG, Truman C, Dittmer I, Donaldson C, Laundy G, Dudley J, Hows J, Bradley BA (2000) Quantitation of cyclosporin-A sensitive and resistant allospecific cytotoxic cells at birth. Transplant Int (this volume)

7. Hirata M, Cho YW, Cecka JM, Terasaki PI (1996) Patient death after renal transplantation – an analysis of its role in graft outcome. Transplantation 61: 1479–1483
8. Lindholm A, Kahan D (1993) Influence of cyclosporin pharmacokinetics, trough concentrations and AUC monitoring on outcome after kidney transplantation. Clin Pharmacol Ther 54: 205–218
9. Scornik JC, Cecka JM (1996) Immune responsiveness and renal transplantation. In: Cecka JM, Terasaki PI (eds) Clinical transplants 1996. UCLA Tissue Typing Laboratory, Los Angeles, pp 373–379
10. Takemoto S, Terasaki PI (1988) Donor and recipient age. In: Terasaki PI (ed) Clinical transplants 1988. UCLA Tissue Typing Laboratory, Los Angeles, pp 345–356
11. Tesi RJ, Elkhammas EA, Davies EA, et al (1994) Renal transplantation in older people. Lancet 343: 461–464
12. Vail A, Gore S, Bradley BA, et al (1997) Conclusions of the corneal transplant follow up study. Br J Ophthalmol 81: 631–636