LETTER TO THE EDITORS

Successful kidney transplantation in highly sensitized, ultra-long-term dialysis patients

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Dear Editors,

Achieving successful kidney transplantation for highly sensitized patients is a global challenge. These individuals face inequity of access to organs as a consequence of their HLA antibody status; this equates to a prolonged wait time on dialysis, a mounting burden of comorbidity and an increased risk of death [1–3]. Kidney allocation policies across the world aim to address this by prioritizing highly sensitized patients for compatible kidney offers [4–6]. Despite this, those who wait the longest for a kidney transplant remain the most highly sensitized.

Northern Ireland has reported excellent outcomes after kidney transplantation but has traditionally adopted a conservative approach to immunological risk [7,8]. In 2006, the median waiting time for kidney transplantation was the second longest in the UK (1737 days); there were eleven patients who had spent more than a decade on the waiting list (Table 1). All had a calculated panel reactive antibody (cPRA) ≥98%.

HLA antigens were listed as unacceptable mismatches if the corresponding IgG had been detected either currently or historically. To improve the chance of an offer, HLA specificities were delisted as unacceptable if they were not anticipated to result in a current positive CDC cross-match. Luminex single antigen assays and CDC cross-matching were used to facilitate these decisions; however, given the limitations in correlating MFI with cross-match results, decisions were not based on a specific MFI cut-off. In addition, there was a reduced threshold for delisting unacceptable HLA specificities which were common in the UK population or commonly in linkage disequilibrium with the patient's HLA. Following an offer, prospective flow and CDC cross-matches were performed using current and peak HLA donor-specific antibody (DSA) serum samples. Post-transplant HLA antibody testing was undertaken. All recipients received a kidney transplant within 12 months. Demographics are reported in Table 1.

One year after transplantation, there have been no deaths and no cases of antibody-mediated rejection; no recipient has currently got detectable DSA with MFI >1000. Six patients had indication graft biopsies performed; the remaining five were not biopsied and have excellent graft function (creatinine 100–150 μmol/l and no proteinuria). One patient had acute cellular rejection which resolved with treatment with intravenous methylprednisolone. Ten individuals have a functioning kidney transplant; the median creatinine is 132 μmol/l. In addition to one recipient with primary nonfunction, another experienced graft failure within 6 months attributable to multiple insults to an old kidney. This recipient was relisted and received a kidney transplant 4 months after returning to dialysis with an excellent outcome. A limitation of this report is the relatively short follow-up time of these recipients. However, the absence of antibody-mediated rejection and proteinuria and acceptable graft function provides hope for reasonable graft longevity in this cohort of patients whose life expectancy will undoubtedly be shortened by many years spent on dialysis.

This approach has been extended to other highly sensitized patients who have not yet accrued a prolonged waiting time. As a consequence, there is currently only one patient in Northern Ireland with a wait time exceeding 5 years. The current median waiting time is 315 days.

National organ allocation bodies have sought to enhance the access of highly sensitized patients to transplantation. For the maximum benefit to be gained from these schemes, however, dialogue must take place at a local level to establish the acceptable immunological risk in each case. Despite the absolute priority assigned to patients waiting longer than 7 years for transplantation in the UK allocation system, Belfast (NI) is the only centre that has no patients waiting longer than this time [9]. The removal of carefully selected HLA antigens

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Table 1. Demographics of the recipients and details of transplantation.

	Gender	Age/ years	Time on dialysis/ years	Wait time/ years	cPRA/%	Modified cPRA	Comorbidities	Donor type	Historic positive cross-match	Current flow cross-match	Peak cum MFI to DSA*	Current cum MFI to DSA	Induction†	Creatinine at 1 year/ µmol/l	Urinary ACR at 1 year/mg/ mmol
1	Male	23	22.8	22.8	100	79	Coagulopathy, duodenal ulceration	Living (UKLKSS)	CDC	Negative	57‡	Negative	Alemtuzumab	N/A	N/A
2	Female	41	20.3	17.3	100	100	Sclerosing peritonitis with peritonectomy	Living	Flow	Positive	6952	4859	Alemtuzumab plasma exchange	133	1.1
3	Female	65	17.9	16.0	98	98	Hypertension, phaeochromocytoma (resected), splenectomy, diverticular disease	Living	Flow	Negative	5154	Negative	Rituximab	159	0.7
4	Male	46	15.9	15.4	100	100		DBD (EC)	CDC	Negative	12 654	Negative	Alemtuzumab	212	0.6
5	Female	31	16.7	14.9	98	69	Sclerosing peritonitis	DBD	None	Negative	Negative	Negative	Basiliximab	132	0.1
6	Female	62	14.3	14.3	100	90	Antiphospholipid syndrome, bowel infarction, diverticular disease, ischaemic heart disease	DBD (EC)	CDC	Positive	11 463	9074	Alemtuzumab plasma exchange	N/A	N/A
7	Male	32	15.6	14.2	98	98	Venous thromboembolism	DBD	Flow	Negative	3860	Negative	Alemtuzumab	124	0.3
8	Male	56	15.8	13.8	99	61	Hypertension	Living	Flow	Negative	41‡	876	Rituximab	97	0.4
9	Female	66	12.1	12.1	98	87	Ulcerative colitis	DBD	Flow	Negative	12 027	824	Basiliximab	106	1.3
10	Male	54	16.7	11.6	100	82	Hypertension, hypogammaglobulinaemia	DBD	CDC	Negative	14 550	Negative	Alemtuzumab	141	1.4
11	Female	66	10.0	10.0	99	98	Hypertension, atrial fibrillation	DBD (EC)	Flow	Negative	12 728	6525	Basiliximab	125	4.6

UKLKSS, via UK Living Kidney Sharing Scheme; EC, extended criteria; ACR, albumin creatinine ratio.

*Cumulative MFI of antibodies to donor HLA mismatches. Result was considered negative if all MFI to mismatches <800.

†Alemtuzumab was the induction agent of choice in patients with historic positive CDC cross-matches or strongly positive flow cross-matches. Rituximab was used in two living donor transplants and administered 6 weeks prior to transplantation. In deceased donor transplants without an historic positive CDC cross-match, basiliximab induction was administered. Plasma exchange was administered if the current flow cross-match was positive (continued after transplantation in one case only; no other additional therapy was required in any patient).

‡At the time these samples were obtained, antibody testing was performed on a solid phase assay by flow cytometry. These results are reported as CFI.

from the unacceptable mismatch list allows these already prioritized patients to receive donor offers. It is then possible to achieve successful transplantation for this disadvantaged group.

Conflict of interest

The authors have no conflicts of interest to declare.

REFERENCES

1. Bostock IC, Alberu J, Arvizu A, *et al.* Probability of deceased donor kidney transplantation based on % PRA. *Transpl Immunol* 2013; **28**: 154.
2. Fuggle SV, Martin S. Tools for human leukocyte antigen antibody detection and their application to transplanting sensitized patients. *Transplantation* 2008; **86**: 384.
3. Iseki K, Tozawa M, Takishita S. Effect of the duration of dialysis on survival in a cohort of chronic haemodialysis patients. *Nephrol Dial Transplant* 2003; **18**: 782.
4. OPTN. Policy 8: allocation of kidneys. Organ Procurement and Transplanation Network (OPTN) Policy 8: Allocation of Kidneys. https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf
5. NHSBT. Improving access to transplant for long waiting kidney patients, 2013.
6. Heidt S, Witvliet MD, Haasnoot GW, Claas FH. The 25th anniversary of the Eurotransplant Acceptable Mismatch program for highly sensitized patients. *Transpl Immunol* 2015; **33**: 51.
7. Courtney AE, McNamee PT, Maxwell AP. The evolution of renal transplantation in clinical practice: for better, for worse? *QJM* 2008; **101**: 967.
8. McCaughan JA, Courtney AE. The clinical course of kidney transplant recipients after 20 years of graft function. *Am J Transplant* 2015; **15**: 734.
9. NHS Blood and Transplant Annual Report on Kidney Transplantation 2016. http://www.odt.nhs.uk/pdf/organ_specific_report_kidney_2016.pdf.