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ORIGINAL ARTICLE

Tailored desensitization strategies in ABO blood group antibody incompatible renal transplantation

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Conflict of Interest
AD has received grants from the Medical Research Council UK, Roche Organ Transplantation Research Foundation and Roche Pharmaceuticals for the RituxiCAN-C4 (Study of Rituximab to Treat Chronic Renal Transplant Rejection, NCT00476164) and allied studies.
NM is Chief Investigator and ANRB is a Co-Investigator of the ongoing randomized, controlled clinical trial, ReMIND (RituxiMab INDuction in renal transplantation, NCT01095172). NM has received a research support grant from Astellas Pharma Ltd for the ReMIND trial.

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Summary

ABO blood group incompatible renal transplantation, using desensitization procedures, is an effective strategy. Efforts have been made to reduce desensitization: these are usually applied to all patients indiscriminately. The Guy's Hospital ABO blood group incompatible desensitization regimen uses a tiered approach, tailoring strategy according to initial antibody titres. Sixty-two ABO blood group incompatible living donor transplant recipients were compared with 167 recipients of blood group compatible living donor renal transplants. There were no statistically significant differences in allograft survival rates at 1 or 3 years post-transplant, rejection in the first year post-transplant or renal function in the first 3 years post-transplant. There was a higher rate of death in ABO blood group incompatible transplant recipients – this could be associated with differences in age and HLA mismatch between the two groups. Four ABO blood group incompatible patients experienced antibody-mediated rejection (no episode was associated with a rise in ABO blood group antibodies). Of the patients who received no desensitization, or rituximab alone, none has experienced antibody mediated rejection or experienced allograft loss. Tailoring the use of desensitization in ABO blood group incompatible renal transplantation according to initial ABO blood group antibody titres led to comparable results to blood group compatible transplantation.

Introduction

ABO blood group incompatible (ABOi) renal transplantation is an effective strategy for increasing the pool of potential living donors for patients without a suitable antibody compatible donor. Typically, centres that perform ABOi transplantation use protocols containing two elements: an intervention to prevent the return of antibodies

post-transplantation plus antibody removal in the immediate pretransplant period. Although termed 'desensitization' in this field, these interventions do not desensitize in the immunological sense but they are usually sufficiently effective to prevent the hyperacute or acute antibody mediated rejection (AMR) that would result from the untreated presence of pre-existing antibodies in the immediate post-transplant period.

In the early days of ABOi renal transplantation, splenectomy was considered the mandatory intervention to prevent return of antibodies post-transplantation [1]. Since then, desensitization techniques have been refined. Rituximab was first used in the context of ABOi renal transplantation [in combination with double filtration plasmapheresis (DFPP) and splenectomy] in 2002 [2]. The first description of the use of rituximab in place of splenectomy came from Stockholm in 2003 [3], and this strategy has now become widespread [4–19]. Typically, the target is for an antibody level of ≤8 on the day of transplantation [15], because higher levels have been associated with higher rates of AMR [20].

As experience in ABOi renal transplantation has grown, attempts have been made to reduce the degree of desensitization administered, either by reducing the dose of rituximab [16,18], omitting it entirely [21,22], or by modifying the amount of antibody removal used. The number of sessions of immunoadsorption (IA) given post-transplant has been reduced by adoption of an on-demand strategy [23], and the number of pretransplant IA sessions has been varied according to initial anti-ABO blood group antibodies [24]. This last study is the first to report any modification to the desensitization protocol according to initial antibody titres. The majority of centres use the same protocol regardless of the initial titre. Since 2008, our centre has used a regimen which varies both elements of the desensitization strategy (rituximab and antibody removal) according to the starting titre. Our hypothesis is that desensitization strategies can be tailored according to baseline ABO blood group antibody titres and that patients with lower titres require less desensitization. Here, we describe the results of a new approach to ABOi renal transplantation based on this hypothesis: a regimen designed to minimize desensitization based on the initial anti-ABO blood group antibody titres.

Materials and methods

The first ABOi renal transplant at Guy's Hospital was performed on 05 July 2005, after approval of the programme by the management of Guy's and St Thomas' NHS Foundation Trust. This study is a retrospective analysis of prospectively collected data of ABOi transplants performed by the same transplant team at Guy's Hospital, Evelina Children's Hospital and Great Ormond Street Hospital for Children between 01 July 2005 and 30 November 2011. All recipients of ABO blood group compatible (ABOc) living donor transplants performed in the same time period under the pre- and postoperative care of the same team at Guy's Hospital were included as a comparison group. All patients in this study had a negative flow cytometric cross-match (FCXM) prior to transplant.

ABOi transplant recipients all received basiliximab induction and triple maintenance immunosuppression comprising tacrolimus, mycophenolate mofetil (MMF) and steroids (unless there were specific contraindications). Tacrolimus and MMF were started 1 week prior to transplant.

At the beginning of the ABOi transplant programme, all patients received rituximab (375 mg/m^2) 4 weeks prior to transplant, with intravenous immunoglobulin (IVIG, 0.5 g/kg) and pre- and post-transplant antibody removal using Glycosorb-ABO IA columns. The desensitization protocol was subsequently refined to take into account initial antibody titres. From February 2008, routine pretransplant antibody removal was omitted for those with initial titres of 8 or lower, DFPP was used for patients with titres between 16 and 64 and Glycosorb-ABO IA columns for those with titres >64. The planned number of cycles of preoperative antibody removal is judged according to baseline titres, with the expectation of a fall of two antibody dilutions for each cycle.

(The rationale for the use of IA only for those patients with titres >64 is that DFPP is cheaper, albeit with a theoretically higher risk of bleeding. Patients with titres between 16 and 64 require fewer cycles of antibody removal (few enough that it should not significantly affect coagulation parameters); patients with titres >64 will need more cycles of antibody removal. IA is not associated with derangement in coagulation parameters [25], whereas serial DFPP has been shown to lead to a reduction in fibrinogen levels and prolongation of the partial thromboplastin time [26].)

In April 2008, the routine use of IVIG was stopped. From February 2009, rituximab was not given to those patients with titres of <8. The dose of rituximab has remained 375 mg/m^2 throughout the programme. Post-transplant antibody removal [typically plasma exchange (PEX)] is currently used only if there is a significant rise in antibody titres (on-demand) or for allograft rejection. The current strategy is illustrated in Fig. 1.

From October 2010, the use of alemtuzumab in place of rituximab and basiliximab was adopted for patients who had DSA but a negative FCXM, in addition to ABO blood group incompatibility. In three patients, Therasorb Therapeutic Apheresis was used in addition to or in place of Glycosorb-ABO IA columns.

At the start of the study period, standard immunosuppression for ABOc transplant recipients was basiliximab induction and triple maintenance immunosuppression comprising cyclosporine, MMF and steroids. In 2009, the protocol changed so that tacrolimus was used in place of

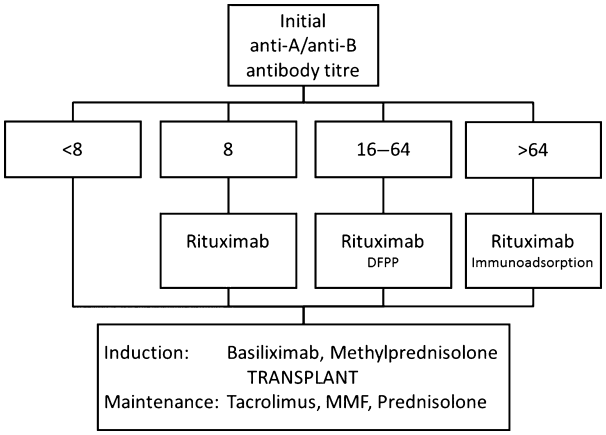

Figure 1 Guy's Hospital minimal desensitization strategy. This is the current strategy. Because of the evolution of the programme, not all patients reported were treated according to this exact protocol. As described in Table 1, seven patients received no desensitization, six patients received rituximab alone, 19 patients received rituximab and DFPP and 14 patients received rituximab and immunoadsorption (three patients received rituximab, DFPP and immunoadsorption).

cyclosporine. Calcineurin inhibitors were started 2 days prior to transplant.

Rejection episodes were defined on the basis of treatment given following a renal transplant biopsy diagnosing rejection according to the Banff criteria (initially 1997 [27] then 2007 [28]). ABOi transplant recipients underwent protocol biopsies at 3 and 12 months post-transplant if there was no recent 'for cause' biopsy and the patient gave consent.

Anti-A and anti-B antibody titres (total immunoglobulin load) were measured by the indirect antiglobulin test (IAT) using gel cards (DiaMed ID-Card Coombs anti-IgG, catalogue number 004025) in a single laboratory.

eGFR was routinely calculated for adult patients in hospital laboratories, using the Modification of Diet in Renal Disease (MDRD) formula.

Statistical analysis

Graft survival times were recorded from date of transplant to date of graft failure, both censored and uncensored for patient death with a functioning allograft. Patients with no record of death or allograft failure were censored at the date of last known function on their last clinic follow-up. No patients were lost to follow-up. Patient survival was determined as time from transplant to time of patient death, censoring at last follow-up where no death was reported. Clinically relevant factors [age, total HLA mismatch, gender, number of previous transplants, pre-emptive transplantation, T-cell mediated rejection (TCMR) or AMR], which may have been associated with the study outcomes, were assessed using univariate tests: categorical variables were compared using the Pearson's chi-squared test. Mann–Whitney *U*-tests were used for continuous variables. Statistical significance was defined at a P-value <0.05. Survival after transplantation was examined with unadjusted Kaplan–Meier survival curves [29] with comparisons between ABOc and ABOi groups made using the log-rank test. Cox proportional hazards regression analysis was applied to investigate the association between the type of transplant and survival, adjusting for potential clinically significant confounding factors. The statistical analysis was performed using 'Statistical Package for the Social Sciences' version 19 for Windows (SPSS, Chicago, IL, USA).

Results

Sixty-two patients underwent living donor ABOi renal transplantation over the time frame studied. This includes three paediatric ABOi transplants. All patients who were listed for desensitization and/or ABOi transplantation were successfully transplanted. 167 ABOc transplants were performed over the same time period.

The direction of blood group incompatibility in the ABOi transplants is illustrated in Fig. 2. The most common incompatibility was blood group A donor with blood group O recipient (28 transplants). All possible incompatible combinations were performed except for blood group AB donor with blood group O recipient.

The distribution of initial A/B blood group antibody titres (prior to any desensitization) is illustrated in Fig. 3, and the desensitization strategies used are summarized in Table 1. Of the 48 patients who received pretransplant antibody removal, the mean number of sessions was 3.9 (SD 2.5). Ten patients received post-transplant antibody removal (mean number of sessions 2.9, SD 1.9), five as routine antibody removal in the early stages of the programme, one for treatment of AMR, one for treatment of thrombotic microangiopathy (TMA), two for a rise in antibody titres (from 16 to 32) in the absence of allograft dysfunction and one for a rise in creatinine (subsequently attributed to TCMR) in the absence of a rise in antibody titres.

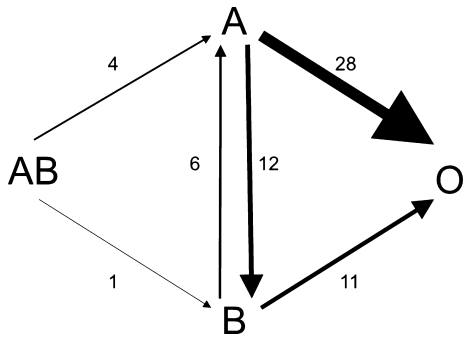

Figure 2 Direction of ABO blood group incompatible transplantation.

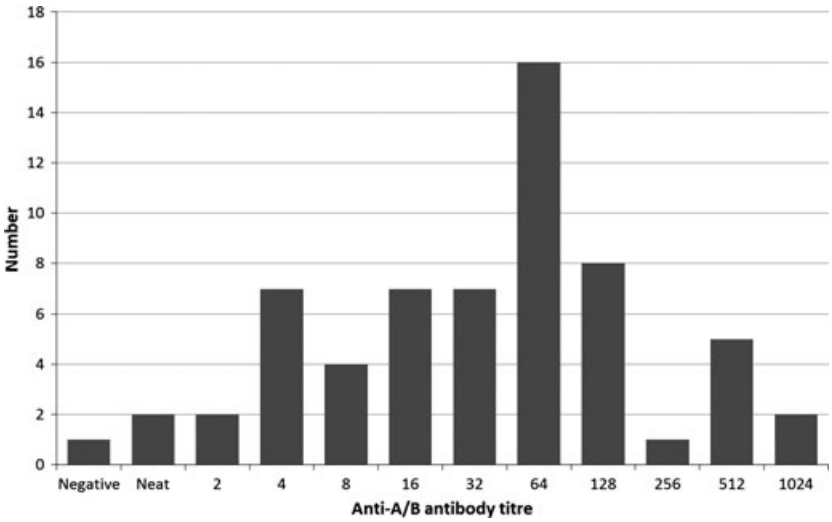

Figure 3 ABOi renal transplant recipients – initial (predesensitization) anti-A/B antibody titres.

Table 1. Desensitization strategies used in ABOi cohort.

No desensitization	7
Pretransplant antibody removal alone	1
Rituximab alone	6
Rituximab and pretransplant antibody removal	33
Rituximab, pre- and post-transplant (on-demand) antibody removal	3
Rituximab, IVIG and pretransplant antibody removal	4
Rituximab, IVIG, pre- and post-transplant antibody removal (5 routine and 1 on-demand post-transplant antibody removal)	6
Alemtuzumab, no pretransplant antibody removal, post-transplant (on-demand) antibody removal	1
Alemtuzumab and pretransplant antibody removal	1

Within the ABOc group, eight patients received rituximab prior to transplantation (as participants in a randomized controlled clinical trial, RituxiMab INDuction in renal transplantation (ReMIND), NCT01095172) and one patient received alemtuzumab on induction in place of basiliximab.

All ABOi patients received tacrolimus initially – one patient was converted to sirolimus. One hundred and eleven ABOc patients (66.5%) received cyclosporine initially; 56 (33.6%) received tacrolimus. Of those patients initially on cyclosporine, 40 patients have remained on cyclosporine, seven have stopped calcineurin inhibitors completely (with five of these commencing sirolimus) and 59 were converted from cyclosporine to tacrolimus (with three of these also receiving sirolimus). Of those, ABOc patients initially on tacrolimus, one stopped calcineurin inhibitors completely and one was converted from tacrolimus to cyclosporine.

The characteristics of the ABOi and ABOc transplant recipients are summarized in Table 2. The mean time of

Table 2. Demographic data of ABOi and ABOc transplant recipients.

	ABOi (n = 62)	ABOc (n = 167)	P-value
Age (Years)	46.7 (SD 15.91)	42.9 (SD 13.35)	0.026*
Sex (Male:Female; % Male)	35:27 (56.5%)	102:65 (61.1%)	0.526†
Time of follow-up (days)	779 (SD 541.42)	1018 (SD 613.20)	0.010*
Number with at least 1 previous renal transplant (%)	13 (21.0%)	31 (18.6%)	0.681†
Pre-emptive	16 (25.8%)	65 (38.9%)	0.048† Pre-emptive v PD v HD
PD	16 (25.8%)	23 (13.8%)	0.065† Pre-emptive v any dialysis
HD	30 (48.4%)	79 (47.3%)	
Total HLA mismatch	3.4 (SD 1.43)	2.7 (SD 1.62)	0.001*
HLA-A mismatch	1.06 (SD 0.62)	0.88 (SD 0.68)	0.059*
HLA-B mismatch	1.19 (SD 0.65)	0.97 (SD 0.67)	0.025*
HLA-DR mismatch	1.15 (SD 0.62)	0.81 (SD 0.69)	0.001*

*Mann–Whitney *U*-test.
†Pearson's chi-squared test.

follow-up of the ABOi group (779 days) was less than that of the ABOc group (1018 days, $P = 0.010$) owing to the fact that there was a continuous rate of ABOc transplants over the time period of the study, whereas the rate of ABOi transplantation has increased over time. Patients in the ABOi group were older than those in the ABOc group (46.8 years vs. 42.9 years, $P = 0.026$). There was a similar frequency of previous transplantation in the two groups (21.0% vs. 18.6%, $P = 0.681$). There was a lower rate of pre-emptive transplantation in the ABOi group than in the ABOc group (25.8% vs. 38.9%), although this difference was not statistically significant ($P = 0.065$). ABOi transplant recipients received less well HLA-matched kidneys than ABOc transplant recipients (Total HLA MM 3.4 vs. 2.7, $P = 0.001$).

Allograft survival

At 1 year post-transplant, death-censored allograft survival was 98.4% (SE 0.016) in the ABOi group and 98.8% (SE 0.009) in the ABOc group (log rank $P = 0.789$). Uncensored allograft survival was 92.9% (SE 0.034) in the ABOi group and 98.1% (SE 0.011) in the ABOc group (log rank $P = 0.060$). At 3 years post-transplant, death-censored allograft survival was 98.4% (SE 0.016) in the ABOi group and 97.9% (SE 0.012) in the ABOc group (log rank $P = 0.970$) – see Fig. 4. Uncensored allograft survival was 90.3% (SE 0.042) in the ABOi group and 96.2% (SE 0.017) in the ABOc group (log rank $P = 0.072$).

Over the time of follow-up, 1 (1.6%) of the 62 ABOi renal transplant recipients experienced loss of their allograft, on day six post-transplant, due to severe postoperative bleeding (from anastomotic dehiscence of the transplant artery) following aggressive combined TCMR and AMR. This patient had an anti-B antibody titre of 256 prior to desensitization and experienced no rise in either anti-B antibody or DSA at the time of rejection (see Table 3). Of the 167 ABOc renal transplant recipients, 3 (1.8%) experienced allograft loss, due to:

1. severe bleeding and allograft rupture (on day 31 post-transplant)

2. transplant infarction following a complication of a radiological procedure for minor transplant renal artery stenosis (on day 135 post-transplant)

3. BK virus nephropathy (on day 605 post-transplant).

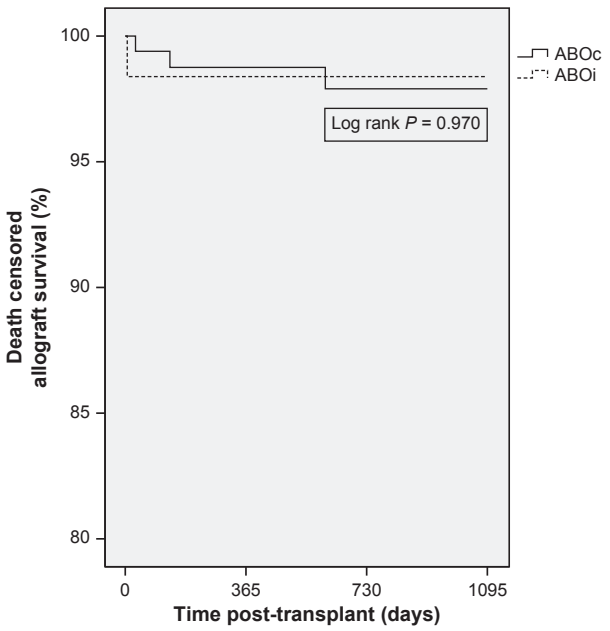

Figure 4 Kaplan–Meier survival curve of death-censored allograft survival at 3 years post-transplant.

Patient survival

At 1 year post-transplant, patient survival was 94.5% (SE 0.031) in the ABOi group and 99.3% (SE 0.007) in the ABOc group (log rank $P = 0.024$). At 3 years post-transplant, patient survival was 91.9% (SE 0.039) in the ABOi group and 98.3% (SE 0.012) in the ABOc group (log rank $P = 0.018$) – see Fig. 5.

Adjustment for the significant differences in age and total HLA mismatch between the two groups using Cox proportional hazards analysis removes any statistically significant difference in patient survival at 1 and 3 years post-transplant, suggesting that these additional factors are influencing differences in survival between the groups.

Over the time of follow-up, 4 (6.5%) of the 62 ABOi renal transplant recipients died, all with functioning allografts, due to:

1. sepsis following severe bleeding as a complication of a bone marrow biopsy to confirm post-transplant lymphoproliferative disorder (PTLD; on day 97 post-transplant). This patient received neither rituximab nor antibody removal prior to transplant.

2. *Pneumocystis jirovecii* pneumonia (PCP; on day 205 post-transplant). This patient received three doses of rituximab (328, 176 and 9 days pretransplant), one course of IVIG and a total of 18 cycles of antibody removal pretransplant (her transplant was cancelled three times – once because of a donor issue, once because of high antibody titres and once because of cellulitis), and a further dose of IVIG and three cycles of antibody removal post-transplant for a rise in antibody titres.

3. PCP (on day 222 post-transplant). This patient received one dose of rituximab and four cycles of antibody removal pretransplant.

4. PCP (on day 629 post-transplant). This patient received one dose of rituximab and three cycles of antibody removal pretransplant.

Table 3. Details of patients who experienced AMR.

Type of transplant	Age	Total HLA MM	Number of previous transplants	Pretransplant calculated reaction frequency (%)	Initial ABO blood group Ab titre	Number of AMR episodes	Time to first AMR episode (days)	Rise in ABO blood group Ab titres at time of AMR	Rise in DSA at time of AMR	FK506 level prior to AMR episode (ng/mL)
ABOi	34	4	0	0	256	1	6	No	No	14
ABOi	38	3	0	83	512	1	7	No	No	13
ABOi	42	2	1	76	4	2	8	No	No	10
ABOi	66	4	0	0	128	1	391	No	No	10
ABOc	46	2	0	80	N/A	3	8	N/A	Yes	7
ABOc	52	1	0	0	N/A	1	998	N/A	Yes	6
ABOc	58	2	0	94	N/A	1	7	N/A	No	12

Calculated reaction frequency is 'the proportion of a pool of 10 000 blood group-identical organ donors [from the NHS Blood and Transplant national database] against which the recipient has HLA antibodies' [50].

These patients had anti-A titres of 4, 128, 1024 and 16 respectively, prior to any desensitization.

There were no episodes of PCP in our ABOc cohort. However, two patients from our centre who received deceased donor renal transplants did die from PCP, and many renal units in the United Kingdom experienced an increase in the rates of PCP between 2008 and 2010 [30].

Of the 167 ABOc renal transplant recipients, 4 (2.4%) died, again all with functioning allografts, due to:

1. complications of a massive pulmonary embolus (on day 248 post-transplant).

2. Recurrent metastatic squamous cell carcinoma of the vulva (on day 866 post-transplant).

3. Glioblastoma multiforme (on day 1449 post-transplant).

4. Oesophageal adenocarcinoma (on day 2001 post-transplant).

Rejection episodes

ABOi renal transplant recipients underwent a greater number of renal transplant biopsies than ABOc renal transplant recipients (1.81 vs. 1.23, $P = 0.008$). This was primarily due to the protocol biopsy regimen instituted for the ABOi patients which is not in place for the ABOc patients.

No statistically significant differences were found in rejection rates at 1 year post-transplant between the ABOi and

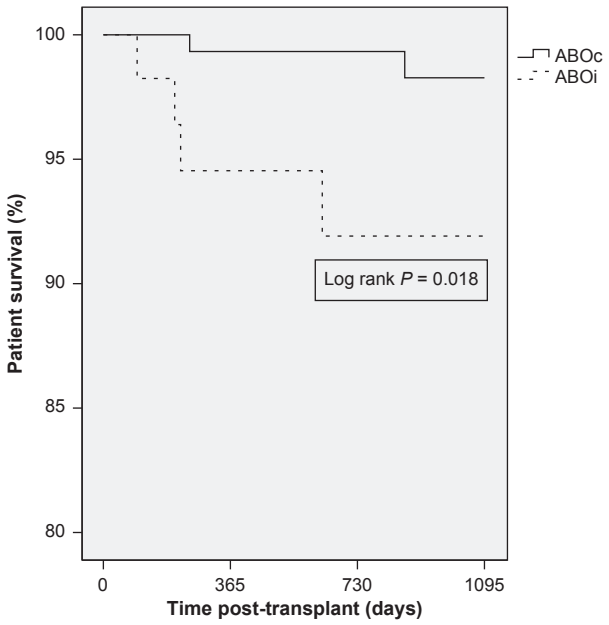

Figure 5 Kaplan–Meier survival curve of patient survival at 3 years post-transplant.

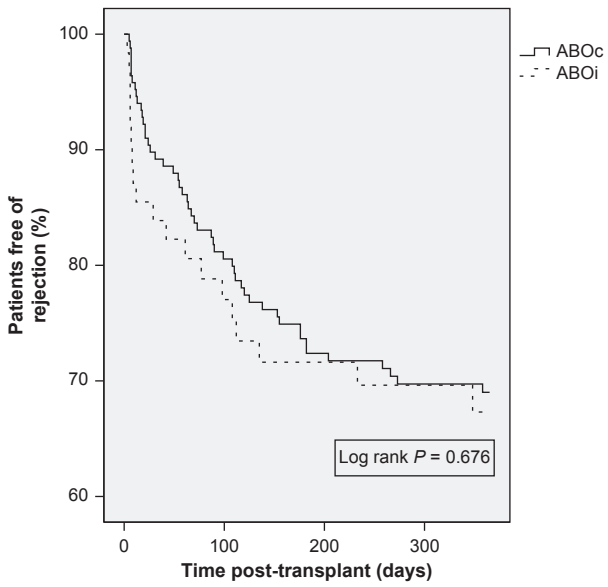

Figure 6 Kaplan–Meier survival curve of rejection-free survival 1 year post-transplant.

Table 4. Renal function of ABOi and ABOc transplant recipients.

	ABOi (n = 62)	ABOc (n = 167)	P-value*
1 year creatinine	151.45 (SD 80.19) n = 42	133.34 (SD 47.51) n = 134	0.368
2 year creatinine	139.44 (SD 59.49) n = 32	137.21 (SD 42.62) n = 101	0.854
3 year creatinine	131.82 (SD 34.11) n = 17	136.76 (SD 53.95) n = 75	0.888
1 year eGFR	47.15 (SD 20.16) n = 40	50.68 (SD 15.35) n = 134	0.188
2 year eGFR	46.50 (SD 15.19) n = 30	48.53 (SD 14.63) n = 101	0.732
3 year eGFR	47.44 (SD 13.90) n = 16	49.71 (SD 14.20) n = 75	0.494

*Mann–Whitney U-test.

ABOc recipients. Seventeen (27.4%) ABOi patients experienced at least one episode of TCMR, compared with 49 (29.3%) ABOc patients (P = 0.775). Three (4.8%) ABOi patients experienced at least one episode of AMR within the first year, compared with 2 (1.2%) ABOc patients (P = 0.124; see Table 3 for further details of those patients who developed AMR, and Fig. 6 for a Kaplan–Meier survival curve of rejection-free survival at 1 year post-transplant).

Renal function

No statistically significant differences were seen in renal function (of those patients with functioning allografts) between the ABOi group and the ABOc group at 1, 2 or 3 years post-transplant (see Table 4).

Results of tailored desensitization

Of the seven patients who received no desensitization (with a mean follow-up of 466 days), one has died with a functioning allograft (Patient 1 in the Patient Survival section above, who died following a bone marrow biopsy). The remaining six patients are all alive with functioning allografts. None of these patients has had an episode of AMR. Three of the seven patients have had at least one episode of TCMR (with the first episodes occurring 61 days, 108 days and 112 days post-transplant).

Of the six patients who received rituximab alone (with a mean follow-up of 874 days), all are still alive with functioning allografts. None of these patients has had an episode of AMR. Two of the six patients have had an episode of TCMR (with these episodes occurring 42 and 77 days post-transplant).

Only five patients required on-demand post-transplant antibody removal. Of these, one died with a functioning allograft; the other four are alive with functioning allografts.

Discussion

In this single-centre series comparing ABOi renal transplant recipients and a contemporaneous group of ABOc renal transplants, both groups received similar maintenance immunosuppression regimens. The ABOi programme has developed over time to include tailoring of both rituximab and antibody removal according to the initial antibody titres, with less or even no desensitization used for those with low initial antibody titres. There was similar renal function, rate of TCMR and allograft survival in the two groups. There was a higher rate of unadjusted death in the ABOi group compared with the ABOc group. This difference was statistically significant. The ABOi renal transplant recipients were older and had a greater degree of HLA mismatch with their donors than the ABOc transplant recipients. Cox proportional hazards analysis adjusted for these important prognostic factors and eliminated the difference in patient survival between the two groups. It is therefore possible that the difference in mortality is a result of the different demographics of patients who underwent ABOi transplantation, rather than a direct result of the ABO blood group incompatibility itself.

Three patients died as a result of PCP infection. One of these patients received three doses of rituximab, pre- and post-transplant IVIG and antibody removal because of a combination of events leading to the cancellation of her transplant three times – it is possible that her PCP was related to a large immunosuppressive burden. It is also possible that the desensitization strategy, including rituximab, was a predisposing factor in the other two deaths from PCP. However, there is no clear evidence in the literature that rituximab increases the risk of PCP. There have only been three reported cases of an association between rituximab and *Pneumocystis* pneumonia [31,32]. Although some centres have reported the possibility of rituximab increasing infectious complications [14,33,34], concerns have been raised about methodological flaws [35] and account has not been taken of the contribution of numerous other immunosuppressive drugs given in conjunction with rituximab. Many case series examining the same area have found no differences in infection rates [36–40]. Randomized controlled trials examining the use of rituximab in acute rejection [41] or as induction therapy [42,43] have also found no differences in infection rates. Because of the retrospective nature of this study, it was not possible to collect accurate

information concerning nonfatal infections. Moreover, as outlined in the Results section, there was an increase in PCP rates throughout the United Kingdom [30], and rituximab was not identified as a risk factor. The infection did not occur in our group of living donor ABOc renal transplant recipients, but there were cases of infection and death in deceased donor transplant patients at Guy's Hospital who had not received rituximab or any other desensitization.

There was a higher rate of AMR in the ABOi group than in the ABOc group (although the number of episodes in both groups was low). None of these AMR episodes corresponded with a rise in anti-blood group antibody titres, nor in DSA. It is possible that these rejection episodes related to either minor blood group antibodies, other non-HLA antibodies, or to anti-blood group antibodies without a detectable rise in titres (perhaps because of absorption by the renal endothelium). This phenomenon requires further investigation.

The tailored approach described in this article involves changes to both elements of the desensitization strategy (rituximab and antibody removal). Modifications to one or other of these elements have been reported in other centres. Norden *et al.* [44] attempted risk stratification of ABOi renal transplant recipients according to the donor blood type, administering rituximab only to those patients receiving a blood group A1 kidney. However, one recipient with an anti-B antibody titre of 32 experienced loss of a blood group B kidney due to severe AMR. Some centres eschew the use of rituximab entirely, regardless of antibody titre. Johns Hopkins Comprehensive Transplant Center, USA [21] currently use just plasmapheresis and IVIG for ABOi renal transplantation. (However, IVIG is an expensive therapy which is currently difficult to obtain.) Imperial Kidney and Transplant Centre, UK [45] use alemtuzumab in place of rituximab, daclizumab and MMF (although 9.1% of this ABOi cohort experienced AMR in the first year post-transplant). The Royal Melbourne Hospital, Australia [22] have used only antibody removal to ensure low antibody levels prior to transplantation.

Rituximab has become one of the mainstays of treatment in ABOi transplantation. Centres that use rituximab have reported excellent results (summarized in [46]). It has been suggested that its use may lead to higher rates of allograft survival and lower rates of rejection compared with no rituximab [17] (although the results from this study did not reach statistical significance).

University Hospital Freiburg, Germany have introduced a programme of on-demand postoperative antibody removal [23], where seven of 32 (22%) patients required postoperative IA. In comparison, after stopping routine post-transplant antibody removal in our programme, only very few patients (five of 57 (9%)) required antibody removal. In a similar way to other centres [21,24,45], we modify the number of preoperative antibody removal sessions based on the initial antibody titres. We have refined our desensitization strategy further by omitting antibody removal for those with titres of 8 or lower, and also by modifying the type of antibody removal, using DFPP for those with titres of 16–64 and IA for those with titres >64.

Low initial levels of anti-A antibody may be related to allograft survival in A2 to O renal transplantation [47]. Although there are interlaboratory differences in titre measurements [48], many centres have reported that the distribution of anti-A/B antibody titres in patients referred for ABOi renal transplantation prior to any desensitization approximates to a normal distribution [49]. A proportion of patients are therefore receiving ABOi renal transplants with initial antibody titres ≤8 (which is the level generally accepted to be safe to proceed with on the day of transplantation [15]).

Thirteen patients from our ABOi cohort with initial antibody titres ≤8 received no pre- or post-transplant antibody removal, and seven of these received no desensitization at all. None of these patients experienced AMR or lost their allografts. Only one patient died, from a cause unrelated to the ABO blood group incompatibility. This is a relatively small group of patients, but the outcomes in this group suggest that patients with low initial antibody titres can be managed successfully using a minimal desensitization strategy.

In conclusion, most centres performing ABOi renal transplantation have a protocol that if the antibody titre after desensitization on the planned day of surgery exceeds a certain value (such as 8), then the transplant will be delayed; if the antibody titre on referral to the ABOi programme is already at or below that value, desensitization will be administered. We take a different approach and do not use any desensitization if the antibody titre is 4 or lower. Furthermore, we use a tiered approach for antibody titres of 8 or more, so that we minimize desensitization based on initial anti-ABO blood group antibody titres. This approach to ABOi renal transplantation leads to similar outcomes to ABOc transplantation.

Authorship

NM, RV and AD: initiated the paper. ANRB, MM, MN and SK: collected data. VGH and ANRB: analysed the data. ANRB: produced an initial draft. All authors participated in discussion, review/revision and approval of the final version prior to submission.

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