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ORIGINAL ARTICLE

Discontinuation of steroids in ABO-incompatible renal transplantation

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SUMMARY

A steroid-free protocol for ABO-compatible renal transplantation has been used at our center since 1983. To minimize the adverse effects of steroids, we also developed a steroid sparing protocol for ABO-incompatible renal transplantation in 2008. The present study is a report of our results. A retrospective review of the first 50 ABO-incompatible renal transplantations performed at a single university center. If no immunological events occurred in the post-transplant period, prednisolone tapering was initiated approximately 3 months after transplantation. Forty-three patients completed prednisolone tapering after 289 ± 58 days. Three patients died during follow-up, and four patients lost graft function. None of these adverse events were rejection related. Eleven patients experienced rejections; seven were on prednisolone and four were after weaning from prednisolone. All patients responded well to antirejection treatment. Overall, 1-year rejection rate was 19%. One- and 3-year graft survival was 94% and 91%, respectively. One-year post-transplant median serum creatinine was 123 μmol/L. We found acceptable rejection rates, graft survival, and creatinine levels in patients undergoing ABO-incompatible renal transplantations with a steroid sparing protocol. However, a longer follow-up of a lager cohort is needed before firm conclusions can be made.

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Introduction

Renal transplantation is the most effective treatment option for patients with chronic kidney disease. ABO-incompatible (ABO-i) living donor renal transplantation is now accepted as a suitable alternative when there is no acceptable ABO-compatible (ABO-c) donor. Due to excellent outcomes for both patients and grafts, the number of patients receiving an ABO-i kidney graft is increasing worldwide [1,2]. Because of the pretransplant circulating anti-A and/or anti-B antibodies, ABO-i renal recipients are at risk for acute blood group antibody-mediated rejection (AMR) and multiple strategies are required to prevent this complication. Up till now, a number of protocols have been developed.

A Swedish ABO-i renal transplantation program was the first to successfully combine new treatment modalities

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as rituximab, antigen-specific immunoadsorption (IA), and intravenous immunoglobulins (IVIG) into a highly effective pretreatment protocol [3]. Published data have shown remarkable good short- and long-term results of this protocol [4,5].

As experience in ABO-i renal transplantation has accumulated, attempts have been made to reduce the degree of desensitization administered either by reducing the dose of rituximab or by modifying the amount of antibody removal used. The number of pretransplant IA sessions has varied according to initial titer of anti-ABO blood group antibodies [6,7]. Furthermore, the number of sessions of IA given post-transplant has been reduced by adoption of an on-demand strategy [8]. With these encouraging outcomes, further improvements of modern protocols aim at minimizing toxicity and decreasing overall immunosuppression to reduce the long-term risk of this treatment. Avoidance of steroids would be a desirable goal, due to the well-known negative side effects of steroids like osteoporosis and aggravation of multiple cardiovascular risk factors such as hypertension, dyslipidemia, newly onset diabetes mellitus, and weight gain [9]. These cardiovascular risk factors may have an important negative impact on graft and patient survival [10].

Since 1983, we have successfully used a steroid-free protocol for the ABO-c renal transplantations [11,12]. In the field of ABO-i renal transplantation, there are only limited data concerning early or late steroid withdrawal [13–15]. To determine the success rate and risk of steroid withdrawal after ABO-i renal transplantation, we examined the outcome of the first 50 transplantations in our transplantation center, and compared our results to published outcome for ABO-i renal transplantations without prednisolone withdrawal.

Patients and methods

ABO-i living donor renal transplantation has been performed in our center since 2007. Fifty consecutive ABO-i living donor renal transplantations have been performed until July 2013. All combinations of ABO-incompatibility were accepted. The immunosuppressive protocol consisted of one dose of rituximab (375 mg/m^2) administered 4 weeks before transplantation. This was followed by a conventional triple-drug immunosuppressive protocol consisting of tacrolimus (0.25 mg/kg/day), mycophenolate mofetil (MMF) 2 g daily, and prednisolone 30 mg daily initiated 14 days before transplantation. Postoperatively, the desired tacrolimus level was 15 ng/ml and was reduced to 10 ng/ml and 5 ng/ml after 4 and 8 weeks, respectively. Three months after transplantation MMF were reduced to 1 g daily. Prednisolone dose was increased to 100 mg on the day of transplantation, followed by a daily reduction of 10 mg until reaching a dose of 20 mg per day, which was continued the first postoperative month. This dose was reduced to 15 mg daily and 10 mg daily in the second and third postoperative month, respectively. Afterward, withdrawal from prednisolone was considered.

Routinely, recipients received prophylaxis with sulfamethoxazole/trimethoprim and acyclovir for 3 months except when the donor was CMV-positive and the recipient CMV-negative, than sulfamethoxazole/trimethoprim and valganciclovir was used. After transplantation, the recipients was screen for CMV and EBV infection by polymerase chain reaction (PCR) weekly the first 12 weeks afterward every 3 months. Urine PCR for BK virus was performed the first 2 years every 6th week.

Pre-operatively, the anti-A or anti-B antibodies were removed using antigen-specific immunoadsorption (GlycoSorp ABO; Glycorex Transplantation AB, Lund, Sweden) of double plasma volumes. A detailed description of the apheresis procedure has previously been published [16,17]. The number of immunoadsorptions was dependent on the initial isohemagglutinin titer of anti-A or anti-B antibodies, aiming of a value below 1:32 before transplantation. Normally, three IAs was planed, administered at day 5, 4, and 1 before the transplantation. Antibody removal was omitted for those with initial titers of 1:32 or lower. If the isohemagglutinin titers exceeded 1:256 at screening, five pre-operative IA sessions were planed. If the titer at screening exceeded 1:1000, the donor was considered unsuitable. After the last pre-operative session, all patients were given IVIG 0.5 g/kg. The first two patients received postoperative immunoadsorption of one plasma volume at day 1, 3, and 6, respectively. Based on experiences from other centers [8,18], this strategy was later changed and no postoperatively immunoadsorption was routinely planed.

Induction therapy was only administered in the presence of donor-specific antibodies (DSA). Initially, we used basiliximab but in 2012 we switched to antithymocyte globulin. DSA was measured by Luminex technology with Labscreen beats. In case of DSA of HLA-type with positive cross-match, we did not use the donor.

Protocol biopsy was not performed. Rejection was diagnosed according to the Banff criteria 07.

The following results are collected retrospectively from the medical records.

Statistical analysis

Data were analyzed using GRAFPAD PRISM (GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego, CA, USA). Graft survival was recorded from date of transplant to date of graft failure censored for death. Patients with no record of death or allograft failure were censored at the date of last follow-up. Rejection-free survival was calculated from date of transplant to date of rejection censored for death and graft loss. Patient survival was determined as time from transplantation to patient death censoring at last follow-up where no death was reported. Statistical significance was defined as a P-value < 0.05.

Results

Recipient characteristics

From the beginning of the ABO-i program in 2007 until July 2013, a total of 50 patients received an ABO-i renal transplant from a living donor and the median clinical follow-up was 38 months (interquartile range 19–49). Median transplant recipient age was 50 years, and 66% of the patients were male. A total of 82% were on dialysis at the time of transplantation, and the most common kidney disease was IgA nephropathy.

Seven patients (14%) had DSA. Three were inducted with basiliximab and four with antithymocytglobuline. One patient was inducted with basiliximab in 2011 because the complement-dependent cytotoxic crossmatch turned positive on B cells just before transplantation. Yet another patient was inducted with basiliximab in 2011, the reason for this is not clear. The median number of HLA mismatches was 2:1 (range 0:0–4:2). All incompatible blood groups were represented. There were 16 (32%) patients with high initial isohemagglutinin titer (≥1:256), and three patients had a titer of 1:1000. A median of 3 IAs was performed pre-operatively, with a range of 0–7 sessions.

The clinical and demographical patient characteristics are summarized in Table 1.

Table 1. Clinical characteristics of ABO-incompatible renal transplant recipients.

Patients, *n*	50
Median age [range]	50 years [23–67]
Males/females	33 (66%)/17 (34%)
Kidney disease	
IgA nephropathy	9 (18%)
Hypertension	6 (12%)
Diabetes	5 (10%)
ADPKD	5 (10%)
Other	17 (34%)
Unknown	8 (16%)
Preemptive transplantation	9 (18%)
Dialyses	41 (82%)
0–6 months	4
6–12 months	11
12–24 months	4
>24 months	22
Median HLA mismatch	A = 1, B = 1, DR=1
Incompatible blood groups	A1 = 18, A2 = 9, B = 22, Ax = 1
No. with previous RTX	7 (14%)
Median anti blood group titers	
Pre-IA IgG [range]	64 [2–1000]
Pre-IA IgM [range]	32 [2–512]
Pre-RTX IgG [range]	4 [1–64]
Pre-RTX IgM [range]	4 [1–32]

ADPKD, autosomal dominant polycystic kidney disease; HLA, human leukocyte antigen; Ax, unknown A-subtype; No, number; IA, immunoadsorption; RTX, renal transplantation.

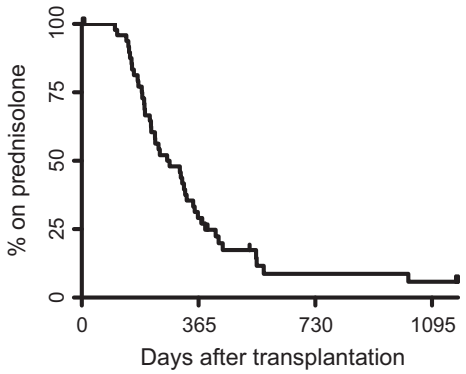

Figure 1 Prednisolone tapering after ABO-incompatible renal transplantation.

Prednisolone

Successful prednisolone tapering was accomplished in 43 patients after 289 ± 58 days (Fig. 1). Prednisolone tapering was initiated at a median of 104 days post-transplant (range 41–356). The first transplanted recipients started tapering at the latest because the protocol was not implemented before 2008. The reason not to switch to a steroid-free regimen in three patients was due to rheumatic disease. The last four patients either died or lost graft function before tapering was initiated.

Patient survival

One- and 3-year patient survival were 96% (95% confidence interval (CI) 91–100%) and 93% (95% CI 85–

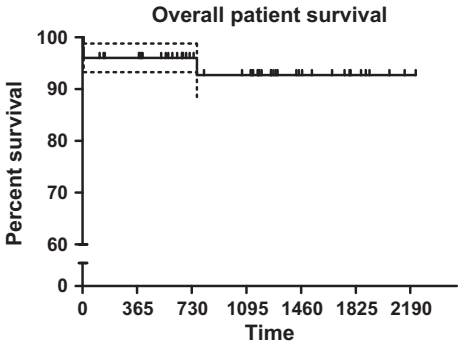

Figure 2 Patient survival rates in days with SE dotted staircase lines after ABO-incompatible renal transplantation.

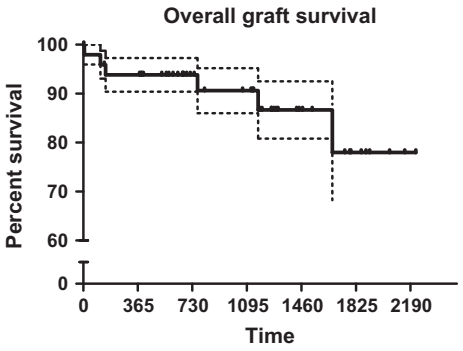

Figure 3 Graft survival rates in days with SE dotted staircase lines after ABO-incompatible renal transplantation.

100%), respectively (Fig. 2). During the observation period, three patients died; one from sudden cardiac death on the third postoperatively day and two from sepsis (27 days and 28 months postoperatively, respectively).

Graft survival

The majority of the patients showed an uncomplicated clinical course and 1- and 3-year graft survival were 94% (95% CI 87–100%) and 91% (95% CI 81–100%), respectively (Fig. 3). Four patients lost graft function, one after unrelated surgery (day 115), one because of recurrence of IgA nephropathy recurrence (day 1170), and two from chronic allograft nephropathy (day 149 and 1667, respectively).

Rejection episodes

One-year rejection rate was 19% (95% CI 8 – 30%) (Fig. 4). All rejection episodes were biopsy-proven. Acute antibody-mediated rejection was observed in two patients at day 2 (HLA antibodies) and day 43 (blood group

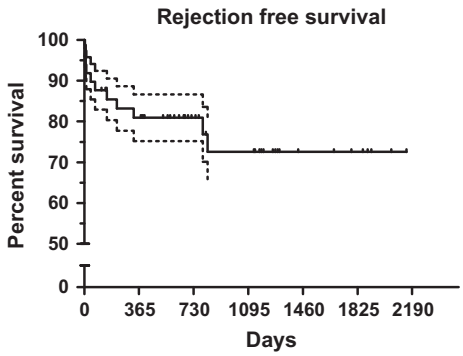

Figure 4 Rejection-free survival with SE-dotted staircase lines after ABO-incompatible renal transplantation.

antibody [19]), respectively. T-cell-mediated rejection occurred in nine patients; five were on prednisolone (one during tapering) and four after weaning from prednisolone. Except for one case, the rejections happened more than 1 year after prednisolone was stopped. In one case, the rejection occurred within 5 months after prednisolone withdrawal. Before the rejection, the patients suffered from a minor infection handled sufficiently with oral antibiotic. Prednisolone was successfully stopped after 6–9 months, except in one case, were the patient was given prednisolone 1 year and 3 months because of the experience of another rejection. All patients responded well to antirejection treatment with intravenous prednisolone. None of the patients with rejection had DSA prior to transplantation. One-year post-transplant median serum creatinine was 123 μmol/l (95% CI 122–171) (Table 2). There was no significant difference

Table 2. Results for ABO-incompatible kidney transplant patients.

Median postoperative serum creatinine μmol/l [range]	
1 week	131 [69–605]
3 months	120 [84–412]
6 months	124 [68–307]
12 months	123 [60–353]
Infection	
CMV infection during follow-up	14 (28%)
EBV infection during follow-up	3 (6%)
BK virus infection during follow-up	11 (22%)
Urinary tract infection 0–3 months post RTX, n	25 (52%)
Patients hospitalized due to infection during the 1-year post-RTX	20 (40%)
Patients hospitalized due to infection during the 2-year post-RTX	9 (20%)

CMV, cytomegalovirus; EBV, Epstein–Barr virus; RTX, renal transplantation.

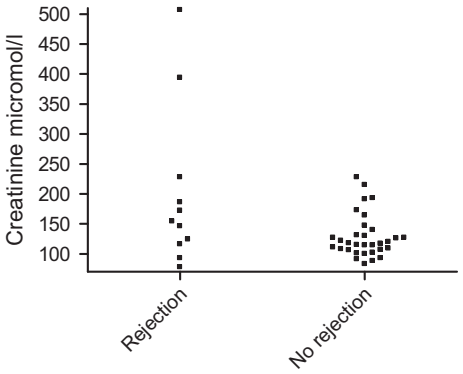

Figure 5 Comparison of creatinine levels between grafts with rejection and no rejection at the latest follow-up. There was no difference in the two groups ($P = 0.08$).

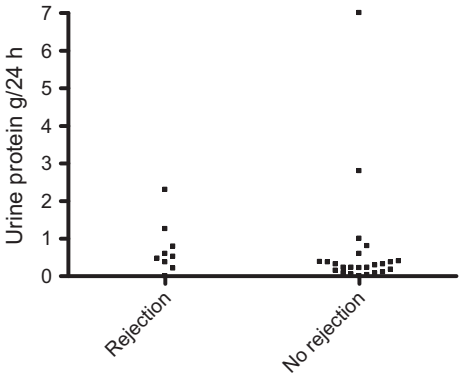

Figure 6 Comparison of proteinuria between grafts with rejection and no rejection at the latest follow-up. There was no difference in the two groups ($P = 0.13$).

at the latest follow-up neither in serum creatinine nor proteinuria between patients with or without previous rejection (Figs 5 and 6).

Infections

Thirty-one patients (62%) were CMV-IgG positive at the time of transplantation. Twenty patients (40%) experienced CMV, BK virus, and/or EBV infection. Eight patients (16%) suffered from more than one type of viral infection. Fourteen patients (28%) experienced CMV infection, six of these also had BK virus infection, but only one had the two infections within a month, initiated by CMV infection. Less intensive immunosuppression cleared both viruses with no signs of later nephropathy. All the CMV infections were within the first 3 months after transplantation and were treated with reduction of MMF dose and/or valganciclovir for a minimum of 21 days, and targeting tacrolimus dosis in the case of high serum concentration. Two of the CMV-infected patient received a CMV-IgG positive kidney while being CMV naïve.

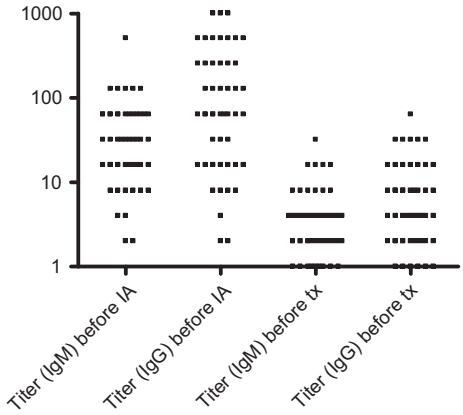

Figure 7 Isohemagglutinin titer IgG and IgM at screening and before transplantation (log scale). IA = immunoadsorption. Tx = transplantation.

One patient experienced biopsy-proven BK virus nephropathy. This was 3 months after transplantation and before prednisolone tapering was initiated. Twenty patients (40%) were hospitalized due to infection during the first year after transplantation, mostly urinary tract infection. None of the infections happened during prednisolone tapering (Fig. 7).

Discussion

In this retrospective single-center study, we evaluated the impact of a steroid sparing regimen on the clinical outcome in a consecutive cohort of ABO-i kidney transplant recipients.

We found that prednisolone withdrawal is possible whenever there is no comorbidity that indicates prednisolone treatment. Other studies on prednisolone withdrawal doing protocol biopsy have not been this successful because of subclinical acute rejection [13]. Their graft survival is however 100%, but the cohort and follow-up period were shorter. The 1- and 3-year graft survival of 94% and 91% is not significantly different from other studies on ABO-i kidney transplantations that we are aware of. In studies with similar immunosuppression regimen but on prednisolone, 1- and 3-year graft survival is found to be 92.9% and 86.7–90.3%, respectively [4,7]. Looking on studies with early or late steroid withdrawal the 1- and 3-year graft survival is found to be 96–100% and 90–100% [13–15,20]. The median serum creatinine was 123 μmol/l 1 year after transplantation and does not differ from

123 to 151 μmol/l as reported by others [4,7,13,14]. It is however worth noting that time and taping regimen of prednisolone in the studies is very different.

All rejection episodes could be treated effectively, and the graft function was not affected by the rejections as judged by serum creatinine and proteinuria. The literature shows very different rejection rates from 7 to 55% [4,7,13–15,20,21]. In our study, we found the 1-year rejection rate of 19% acceptable. The difference in rejection rates is due to differences in immunosuppressive regimens and the fact that some center do protocol biopsies and treat subclinical rejections. Progressive loss of graft function because of ongoing clinical AMR was not observed. Interestingly, the AMR occurred before prednisolone tapering was considered. This is probably because most episodes of acute rejections occur within the first months after transplantation as in other studies [21]. Only one patient experienced rejection during prednisolone tapering. Just before the rejection the patient was switched from MMF to azathioprine because of diarrhea and experienced a urinary tract infection. Prednisolone was later successfully withdrawn from this patient.

IgA nephropathy was the most common kidney disease among our recipients. Histologic recurrence in the allograft, with or without evidence of clinical disease, is common [22,23]. There is no preventive therapy for IgA nephropathy recurrence, and to our knowledge, there are no conclusive data that selection of immunosuppressive therapy alters the risk of recurrence, although some studies show a trend for a decreased risk of graft loss due to recurrent IgA nephropathy associated with the use of steroids [24,25]. We experienced one case of IgA nephropathy recurrence in our cohort. The recurrence was biopsy-proven within the first 14 months after transplantation. The patient was kept on prednisolone 10 mg per day at the time of recurrence because of the aggressive nature of the IgA nephropathy in the native kidneys. The patient was treated with high-dose methylprednisolone and cyclophosphamide but lost graft function at day 1170. In all other cases, prednisolone withdrawal was successful. We do not systematically screen for hematuria, but the creatinine and proteinuria levels after 1 year match our median. One should however notice that IgA nephropathy has a tendency to reappear more than a year after transplantation. In one study, the mean time to recurrence and allograft failure was 31 and 63 months, respectively [23]. Therefore, longer follow-up is needed to firm conclusions.

Patient survival at 1 and 3 year was 96% and 93%, respectively. These survival rates were compatible to other ABO-i renal transplantation studies where 1-year and 3-year patient survival was 94% and 92% in one study [7] and 3-year patient survival 96% in another study [20]. Reported patient survival in ABO-i renal transplantations are few, and in the smaller studies with prednisolone withdrawal and shorter follow-up, the patient survival is reported 100% [13–15].

We used an upper limit for anti-ABO IgG antibody titers of 1:1000 to allow patients to enter our program. This is a higher titer than used in other studies were eligible patients must have isohemagglutinin titers below or equal to 1:256 [20,26]. But the lack of a uniform and reliable test for the measurement of antibody titers hampers comparison to published data. All post-transplantation isohemagglutinin titers remained low. These findings suggest that a high initial isohemagglutinin titer does not increase the risk of AMR. Patients with either high or low initial isohemagglutinin titer showed similar and stable graft function. However, the patient who developed AMR because of blood group antibodies had an initial isohemagglutinin titer of 1:1000.

CMV infection is a serious complication after solid organ transplantation. In our series, CMV infection was observed in 28% of the patients, which do not differ from other studies with CMV rates between 26 and 44% [2].

Fatal infection was observed in two patients. One patient had peritonitis with Enterococcus faecium (peritoneal dialysis prior to transplantation) and the other patient died from Pneumocystis jiroveci pneumonia. Because of the retrospective nature of this study, it was not possible to collect accurate information concerning nonfatal infections.

In conclusion, in ABO-i living donor renal transplantation, prednisolone can safely be tapered 3 months post-transplant without any increase in rejection rates, loss of graft function, or mortality. The ABO-i steroid sparing protocol is especially of value to eliminate side effect of prednisolone in case of osteoporosis, post-transplant diabetes, etc. The major weakness of the study is the small number of subjects and short follow-up period of 38 months. Close monitoring of the ABO-i graft results is mandatory. Our results remain to be confirmed in a large randomized trial with long-term follow-up.

Authorship

MKN: Designed research/study, performed research/study, collected data, analyzed data and wrote the paper. CB: Designed research/study, performed research/study and analyzed data.

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