The Reuse of Immunoadsorption Columns in ABO-Incompatible Kidney Transplantation Is Efficient: The Swiss Experience

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Background. We developed a multicentric Swiss protocol for ABO-incompatible kidney transplantation including immunoadsorption column reuse. The aim of this study was to assess efficacy and safety of immunoadsorption column reuse in ABO-incompatible kidney transplantation. **Methods.** We performed a multicentric prospective trial including all ABO-incompatible kidney transplantations in Switzerland from 2005 to 2011. Patients received rituximab and standardized immunosuppression with tacrolimus, mycophenolate mofetil, and steroids. Antigen-specific perioperative immunoadsorption was performed. Immunoadsorption columns were reused after restoration. Graft survival, patient survival, kidney function, rejections, number of columns, adverse events after column reuse, and anti-A/anti-B antibody titers were assessed. **Results.** Seventy-one ABO-incompatible patients underwent antigen-specific immunoadsorption and could be transplanted across the blood group barrier. Kaplan-Meier estimates for both, patient-censored and death-censored graft survivals were both 97.2% at 5 years. Allograft function was excellent with a mean estimated glomerular filtration rate of 54 mL per min after 1 year. The median number of pretransplant immunoadsorptions was 5. All centers performed column reuse. A total of 394 immunoadsorption procedures were performed with reused filters. Patient survival, graft survival, and adverse events did not differ when filters were reused. Column reuse resulted in cost savings of 21,458 USD per patient. **Conclusion.** We have introduced a national protocol for ABO-incompatible kidney transplantation including immunoadsorption column reuse. Column reuse was efficient and safe.

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The increasing discrepancy between patients on the waiting list and transplanted kidneys has initiated innovative strategies to decrease organ shortage. Regarding living donor kidney transplantation sophisticated protocols to overcome ABO incompatibility were introduced in the past.[1] Initial attempts have been made in the late 1980s in Japan. With improved understanding of the mechanisms of accommodation and antibody-mediated rejection (AMR) and progress in immunosuppression, the results have improved markedly, and are nowadays only slightly inferior or comparable to those of ABO-compatible kidney transplantation.[2-5]

However, the pretreatment of the recipient is elaborate and expensive. Different techniques to remove the blood group antibodies are used, such as the double filtration plasma exchange, regular therapeutic plasma exchange, and nonspecific and specific immunoadsorptions.[6,7] A major advantage of specific immunoadsorption is the efficient depletion of circulating blood group antibodies without considerable losses of protective antibodies and other essential plasma constituents.[8] On the other hand, this treatment is expensive if the immunoadsorption columns are used only once as suggested by the manufacturer.

In Switzerland, we have introduced ABO-incompatible transplantation in 2005, and the involved transplantation centers have agreed on a common protocol using specific immunoadsorption to remove the blood group antibodies. Because of the high costs for the immunoadsorption and additional immunosuppressive medication, we have subsequently introduced a protocol to reuse the immunoadsorption

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columns.[9] We report the results of the Swiss multicenter ABO-incompatible kidney transplantation cohort with a focus on safety and efficacy of the reuse of immunoadsorption columns.

MATERIALS AND METHODS

Patients

This is a multicenter prospective trial that included all patients from transplant centers performing ABO-incompatible kidney transplantation in Switzerland from December 28, 2005 to December 31, 2011. A working group for ABO-incompatible kidney transplantation has been established with representants from all five Swiss transplant centers performing ABO-incompatible kidney transplantation. The working group agreed on one protocol for the desensitization and immunosuppressive treatment. Each center obtained approval for the protocol by the respective local ethical committee (Ref. StV 11-2005). The workup of recipients and donors was performed according to our national and center-specific guidelines.

Male or female patients regardless of age and race, suffering from end-stage renal disease, and fulfilling the general criteria for living donor kidney transplantation were included in the trial. First and repeated kidney transplantations were accepted. All patients gave their written informed consent. Patients were suitable for the protocol if they had a blood group-incompatible living kidney donor with a current negative T-cell and B-cell CDC cross-match (XM) test.

Desensitization and Immunosuppression

A single dose of rituximab (375 mg/m^2) was given 4 weeks before the transplantation. Maintenance immunosuppression with tacrolimus (0.1 mg/kg twice daily), mycophenolate mofetil (1000 mg twice daily, 500 mg twice daily if body weight was less than 50 kg), and prednisone (25 mg once daily) was started before transplantation. Selective blood group antibody removal was performed with a low-molecular carbohydrate column containing A or B blood group antigens linked to a sepharose matrix (Glycosorb; Glycorex Transplantation, Lund, Sweden). Apheresis sessions were performed daily until the immunoglobulin (IgG) and isoagglutinin (IgM) antibody titers against donor erythrocytes were 1:8 or less. The transplantation was then carried out the following day. With each session, at least two plasma volumes were processed. At the beginning of the study, a single dose of IVIG (0.5 g/kg body weight) on day −1 was given; later, IVIG therapy was discontinued. The participating centers were free to give an induction therapy with 20 mg basiliximab on days 0 and 4.

Follow-Up

Blood group antibodies against donor erythrocytes were measured daily for 2 weeks, weekly until day 31 and 3, 6, and 12 months thereafter. At the beginning of study 3, prophylactic apheresis sessions were scheduled after transplantation. Later, apheresis sessions were only performed on demand in case of graft dysfunction and a titer increase greater than 1:8 within the first week or greater than 1:16 within the second week after transplantation. A graft biopsy was performed, and daily immunoadsorption or therapeutic plasma exchange was started in these cases. An isolated increase of blood group antibody titers in the absence of clinical signs of graft dysfunction was not mandatory for the start of apheresis sessions.

Target tacrolimus trough levels were 8 to 10 ng/mL from day −14 to 90, 6 to 8 ng/mL from day 90 to 365, and 4 to 6 ng/mL thereafter. Target mycophenolate mofetil trough level was greater than 2 mg/mL. Steroids (methylprednisolone intravenously and prednisone orally), 500 mg IV on day 0, 250 mg IV on day 1, 100 mg IV on day 2, 50 mg orally from day 3 to 6, 0.5 mg/kg body weight orally from day 7 with a reduction by 5 mg every 2 weeks until 15 mg per day, then by 2.5 mg every 2 weeks until a maintenance dose of 0.1 mg/kg was given. Steroid withdrawal could be considered if the 1-year protocol biopsy revealed no signs of rejection.

Graft Biopsies

Protocol biopsies were performed at 12 months or more frequent according to center policy. Diagnostic biopsies were performed in case of otherwise not explained graft dysfunction using formalin fixation and fresh frozen technique. Staining was performed according to previously described procedures.[10] Biopsies were judged according to the revised Banff criteria 2007 and 2009.[11,12]

Treatment of Acute Rejection

Acute cellular rejection was treated according to local practice with methylprednisolone pulses. In case of suspected or biopsy-proven AMR methylprednisolone (0.5 g intravenously on three consecutive days) was administered. Daily selective immunoadsorption or therapeutic plasma exchange and IVIG could be applied at the discretion of the treating physician.

Detection of Anti–Human Leukocyte Antigen Antibodies and Assignment as Human Leukocyte Antigen–Donor-Specific Antibodies

All sera were tested for class I (i.e., human leukocyte antigen [HLA]-A/B/C) and class II (i.e., HLA-DR/DQ/DP) anti-HLA antibodies using single antigen flow bead assay on a Luminex platform (LabScreen; OneLambda, Canoga Park, CA). A positive result was defined as a baseline normalized mean fluorescent intensity greater than 500. Donor specificity of anti-HLA antibodies was determined by comparison of the anti-HLA antibody specificities with the HLA typing of the donor as previously reported.[5] The CDC-XM assay was performed as reported previously.[13] No prospective flow cytometry-XM was performed. Typing of HLA-antigens was determined by serology (A/B/DR) and/or by sequence specific primer DNA typing (A/B/DR/DQ).

Detection of Blood Group Antibody Titers

Blood group antibody titers were determined against donor-specific erythrocytes by the saline method (IgM) and the indirect Coombs test (IgG) as described previously in detail.[5]

Regeneration of the Columns

Patients with filter reuse were analyzed in a subgroup (filter reuse group). Immunoadsorption columns were regenerated using solutions from Fresenius Medical Care (Redmond, WA). Immediately after the immunoadsorption procedure, the plasma was rinsed out of the column using 1000 mL Buffer PA pH 7.0. After rinsing, the antibodies were eluted with a citrate solution: 1000 mL eluate PA pH 2.2. After elution, the column was neutralized with 1,000 mL buffer PA pH 7.0. Finally, the column (volume, 70 mL) was rinsed

TABLE 1.

IgM and IgG titers for the first use to the third reuse

IgG				
IgG titer	**1° use (N=57)**	**1° reuse (N=57)**	**2° reuse (N=28)**	**3° reuse (N=8)**
0	43 (75.4%)	46 (80.7%)	22 (78.6%)	7 (87.5%)
1	1 (1.8%)	1 (1.8%)	1 (3.6%)	1 (12.5%)
2	5 (8.8%)	2 (3.5%)	2 (7.1%)	0 (0.0%)
4	2 (3.5%)	5 (8.8%)	3 (10.7%)	0 (0.0%)
8	5 (8.8%)	2 (3.5%)	0 (0.0%)	0 (0.0%)
16	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
32	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
64	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
Rank[a]	93.5	67.6	64.5	42.0
IgM				
IgM titer	**1° use (N=57)**	**1° reuse (N=57)**	**2° reuse (N=28)**	**3° reuse (N=8)**
0	6 (10.5%)	19 (33.3%)	9 (32.1%)	6 (75.0%)
1	15 (26.3%)	15 (26.3%)	11 (39.3%)	0 (0.0%)
2	19 (33.3%)	18 (31.6%)	5 (17.9%)	2 (25.0%)
4	9 (15.8%)	2 (3.5%)	2 (7.1%)	0 (0.0%)
8	5 (8.8%)	1 (1.8%)	1 (3.6%)	0 (0.0%)
16	2 (3.5%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
32	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
64	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rank[b]	78.2	74.3	74.9	67.1

[a] P_{Trend}=0.083 (Spearman ρ over the mean ranks).
[b] P_{Trend}=0.333 (Spearman ρ over the mean ranks).
N (%) for columns.
There was no significant difference regarding filter efficacy. Fifty-seven filters were tested after the first use and first reuse, 28 filters after the second reuse, and eight filters after the third reuse.
IgG, immunoglobulin G; IgM, immunoglobulin M.

and filled with 250 mL Immunosorba Preservation Solution containing 0.04% polyhexamethylenebiguanide. The columns were stored in the dark at +2°C to +8°C.

Evaluation of Column Performance After Regeneration

In a subgroup of 57 columns, the performance of the column was systematically evaluated at the end of every immunoadsorption. Blood group antibody titers against the donor's blood group were estimated in the blood taken 10 min before the end of the procedure from the line immediately after the column (Table 1). Negative or low antibody titers indicate efficient antibody removal even at the end of treatment and despite of reuse of the columns. One column revealed a lack of efficacy after the first regeneration in the ex vivo testing. The mean IgG titers of blood group A antibodies were 1.6 after the first reuse (median, 0; range, 0 to 64) and 0.36 (median, 0; range, 0 to 4) after the second reuse. Columns were reused for maximally four times and remained efficient even after multiple reuses. Immunoglobulin G levels appeared to be lower than IgM titers.

Complications

Perioperative complications were graded according the Clavien/Dindo classification.[14] Infectious complications were monitored throughout the whole follow-up period and graded as severe, when a hospitalization was needed. BK and CMV replication were monitored on a routine basis. The CMV disease was defined according to Ljungman et al.[15]

Statistics

Statistical analysis was performed using SPSS for Windows, version 15 (SPSS Inc., Chicago, IL). Kaplan-Meier estimates were calculated, Log rank test and chi-square test to compare groups were applied as appropriate. A two-sided *P* value was considered as statistically significant if less than 0.05.

RESULTS

Patient Characteristics

From September 2005 until December 2011, a total of 80 patients with an ABO-incompatible donor recipient constellation were transplanted in five Swiss transplant centers using a common protocol. Nine patients had additional donor-specific antibodies and were treated with plasma exchange and were therefore excluded from the study. The remaining 71 patients were treated with selective immunoadsorption and included into the analysis. No patient was lost to follow-up. The mean follow-up was 4.2 years. Fifty-two (73%) recipients were men, 19 (27%) were women. The majority had blood group O (64.7 %). The blood group constellations were as follows: 46 patients, A to O; one patient, AB to O, eight patients, A to B; three patients, AB to A, two patients, AB to B, three patients, B to O; and eight patients B to A. The most frequent type of relationship between donor and recipient was married couples, and there was a significantly higher proportion of female donors (45, 63.4%) compared to male donors (26, 36.6%). The mean donor age was 52.5 (±10.7) years, and the mean recipient age was 51.8 (±13.2) years.

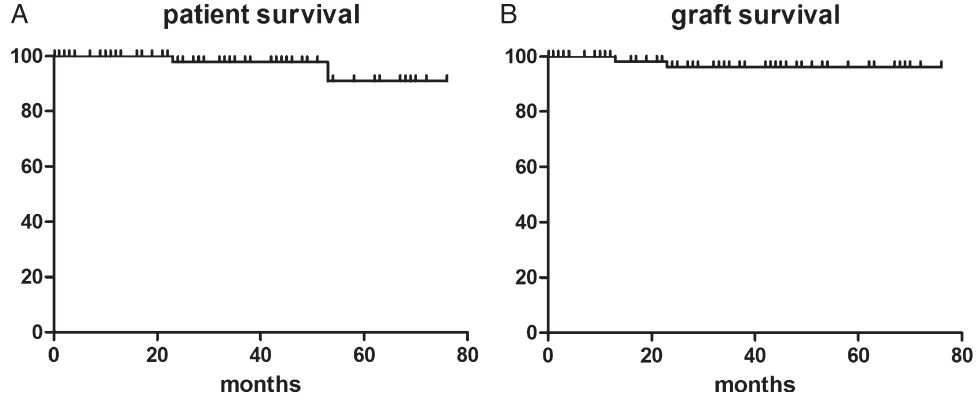

FIGURE 1. Patient-censored (A) and death-censored graft survivals (B) were both 97.2% at 5 years.

Fifty (70%) recipients were on dialysis at the time of transplantation, whereas 30% received a preemptive transplant.

Patient Survival, Graft Survival, and Graft Function

The Kaplan-Meier estimate for patient survival was 97.2% at 5 years (Fig. 1A). The Kaplan-Meier estimates for death-censored graft survival after 1, 2, and 5 years were excellent with 100%, 98.6%, and 97.2%, respectively (Fig. 1B).

The estimated glomerular filtration rate (eGFR) calculated by the chronic kidney disease epidemiology collaboration formula after 1, 2, and 5 years were 54.05 mL per min (±16.03), 52.98 mL per min (±14.48), and 54.0 mL per min (±15.87), respectively. The serum creatinine levels at 1, 2, and 5 years were 126 μmol/L (±39.2), 128 μmol/L (±35.9), and 129.4 μmol/L (±54.6), respectively. The percentage of patients with a pathologic albumin-to-creatinine ratio or protein-to-creatinine ratio over time is given in Figure 2.

Rejection Rate

Thirteen (18.3%) patients developed biopsy-proven acute rejection. The Kaplan-Meier curve for rejection-free survival is given in Figure 3. Among the 13 biopsy-proven acute rejection, three patients had a cellular rejection, whereas 10 had an AMR. The cellular rejections could be treated successfully in all but one case with methylprednisolone pulses. One patient needed antithymocyte globulin. Four patients with AMR had to undergo therapeutic plasma exchange. One patient lost his graft because of early sepsis or caecum perforation and subsequent rejection because of immunosuppression reduction. The majority of rejections occurred early at a mean interval of 4.9 months after transplantation; six rejections occurred within the first month and seven within the first 3 months. At the end of the follow-up period, 25% of the patients were on a corticosteroid-free immunosuppression regimen.

Complications

The overall perioperative complication rate (<30 days) was 26.8% according to the Clavien/Dindo classification.[14] Seventeen percent of all patients experienced severe complications Grad III to IV requiring an intervention or a reoperation. Among these, there were four patients with a septicemia, two patients with a bleeding complication, two patients with a ureteral complication, and four with a lymphocele. All complications occurred exclusively after the transplantation and not during the immunoadsorption period before the transplantation. In the further follow-up, four patients developed cytomegalovirus (CMV) disease and 13 had BK viremia; however, no polyomavirus nephropathy occurred. Two of 71 patients died during the follow-up period. One patient developed a severe donor-derived herpes simplex virus 2 infection and lost his graft. In the further course, he developed multiple complications and died 199 days after transplantation from a complicated pancreatitis. Another patient died 800 days after transplantation from an *E. coli* sepsis with a functioning graft. No complication (infection/fever) occurred during the immunoadsorption therapy before transplantation.

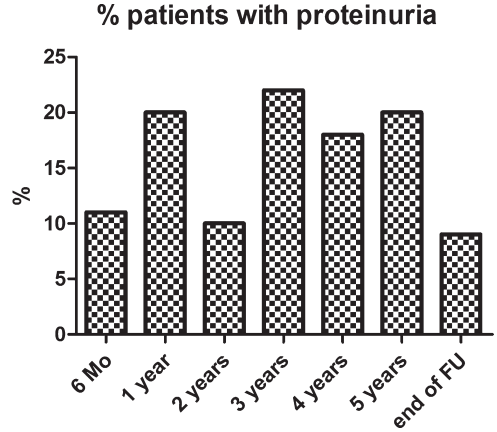

FIGURE 2. The proportion of patients (%) with proteinuria over time and at the end of follow-up.

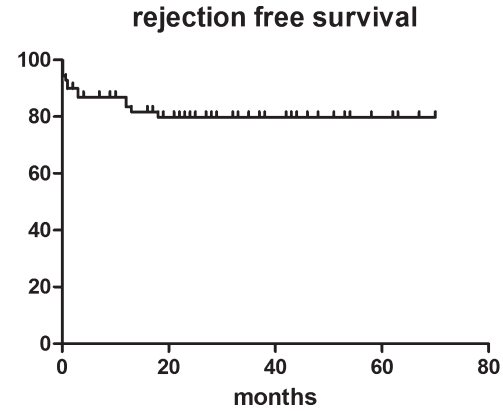

FIGURE 3. The rejection-free survival rate of the cohort with 18.3% of the patients developed a biopsy-proven rejection within the follow-up period.

Selective Immunoadsorption and Reuse of the Columns

Seventy-one patients underwent antigen-specific immunoadsorption treatment. Four hundred twenty-nine immunoadsorption therapies were performed before transplantation and 30 posttransplantation. The specific immunoadsorption successfully lowered the antibody titers in all patients allowing a subsequent transplantation. The median number of immunoadsorptions performed before transplantation was 5 (range, 3–18; Fig. 4A). Nine (12.7%) patients underwent immunoadsorption after transplantation. The median number of immunoadsorptions after transplantation was zero (range, 0–11). The columns were successfully reused in all centers. Overall, we used one to four columns per patient, but only two patients needed more than three columns. We performed a median of three (range, 1–12) immunoadsorptions per column (Fig. 4B). At the introduction of the column reuse protocol, we used more columns per patients also for logistical reasons. One hundred fifty-one columns were used for 459 immunoadsorptions. Using this strategy, we could save 308 columns, which corresponds to 1,523,541 USD (average cost per column 4,946 USD). This corresponds to a saving of 21,458 USD per transplantation.

At the beginning, we assessed the efficacy of the column reuse by checking the antibody titers in the eluate after the column. Details about the first 57 column efficacy tests are given in Table 1. Because the filter reuse efficacy was shown to be reliable, we then focused only on the in vivo antibody titers as a surrogate for the filter efficacy. Furthermore, we performed a subgroup analysis for patients, who were treated

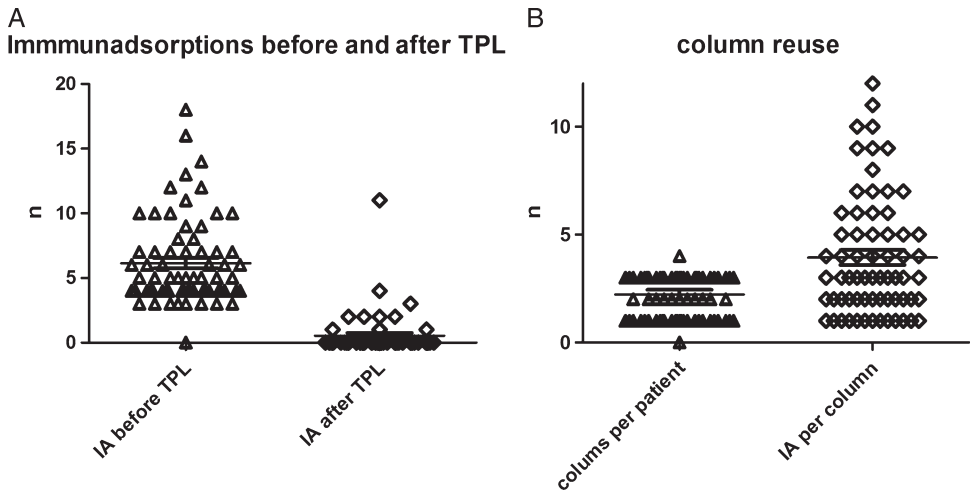

FIGURE 4. A, the number of immunoadsorptions before and after transplantation. The median number of immunoadsorptions performed before transplantation was 5 (range, 3–18). The median number of immunoadsorptions after transplantation was zero (range, 0–11). B, the data about immunoadsorption column reuse. Overall, we used one to four columns per patient and we performed a median of 3 (range, 1–12) immunoadsorptions per column.

with filter reuse. Of the 71 patients, 54 patients (76%) underwent immunoadsorption using filter reuse. A total of 394 immunoadsorption procedures were performed with reused filters. The outcome did not differ from the remaining patients.

The patient survival rate was 98% (95% confidence interval [95% CI], 94% to 100%) in the filter reuse subgroup and 91% (95% CI, 75% to 100%) in the other subgroup (P=0.418). The graft survival was 98% (95% CI, 94% to 100%) in the filter subgroup compared to 91% (95% CI, 75% to 100%) (P=0.435). The rate of acute rejection was 19% (10/53) in the filter subgroup (95% CI, 11% to 31%) and 17% (3/18) (95% CI, 6% to 39%) in the other group (odds ratio 1.13 with 95% CI, 0.29 to 5.86, P=0.870).

The complication rate was 30% in the filter reuse subgroup (95% CI, 20% to 44%) and 22% (95% CI, 9% to 45%) in the other group (odds ratio 1.48 with 95% CI, 0.44 to 6.04, P=0.544). No septicemias and reactions to dissolved filter components similar to first-use syndrome were observed in the filter reuse group.

The eGFR at 1, 2, and 5 years in the filter reuse subgroup were 53.4±15.4 mL per min, 52.4±15.0 mL per min, and 52.7±16.2 mL per min, respectively. The eGFR did not differ from the eGFR in the other subgroup at 1 and 2 years and at the end of follow-up with values of 55.1±17.7 mL per min (P=0.611), 55.2±12.6 mL per min (P=0.575), and 54±14.0 mL per min (P=0.763). No patient treated with a reused filter experienced an infectious complication at the time before transplantation.

Course of Blood Group Antibody Titers and B Cells

The IgG and IgM titers were successfully lowered to antibody titers of less or equal 1:8 before transplantation using specific immunoadsorption (Fig. 5A and B). Reuse of the immunoadsorption columns did not compromise the elimination of the blood group antigens, and no patient was deferred from transplantation because of insufficient lowering of anti-A/B titers. The titers remained low in most of the patients throughout the follow-up period. Only two patients presented with an IgG or IgM titer of more than 1:8 during the follow-up

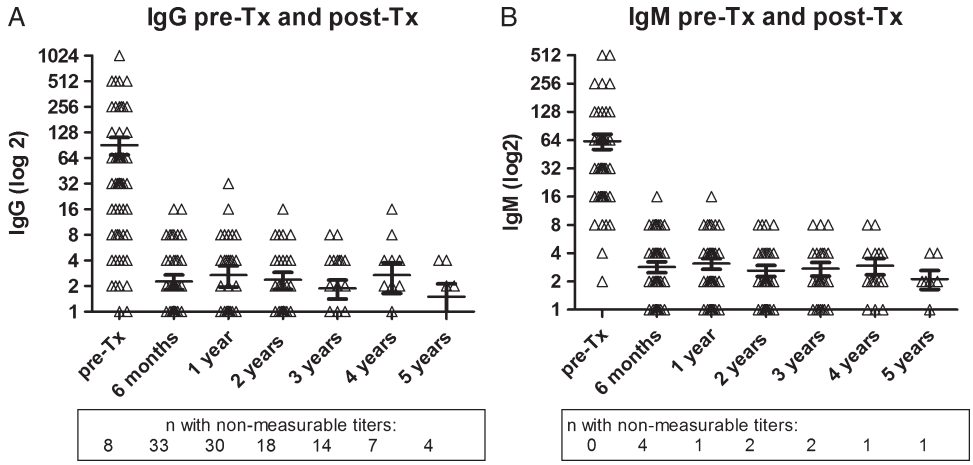

FIGURE 5. The course of the IgG (A) and IgM (B) titers before transplantation and during the follow-up in a logarithmic scale. Patients with undetectable immunoglobulin titers are indicated in the boxes below the graph. IgG, immunoglobulin G; IgM, immunoglobulin M.

period. The mean number of B cells was 98.6 cells/μL (normal range) before transplantation and remained low at a mean of 16.4 cells/μL after 1 year.

DISCUSSION

This is the first report on a multicenter protocol reusing specific immunoadsorption columns for ABO-incompatible kidney transplantation. The protocol has been established and approved by the Swiss ABO-incompatible kidney transplantation group and has been standardized in all transplantation centers across Switzerland. We have shown that the protocol is efficient in reducing the antibody titers and is safe to perform in clinical practice. The results of the multicenter ABO-incompatible cohort are comparable to the results of the available ABO-compatible data in the literature.[1,16] and the Swiss Transplant Cohort Study established since May 2008.

The reuse of the columns did not result in an increased rate of acute rejection or inefficient elimination of blood group antibodies. We observed that the anti-A/B antibody titers and the peripheral B cell pool remained suppressed up to 1 year after transplantation, similar to the findings of Tobian et al.[17]

The protocol for the column reuse was solid and could be successfully used even in centers with small patient numbers. The costs of the peritransplant treatment could therefore be reduced substantially by eliminating the costs for additional columns. Using this strategy, we saved the expenditure of over one million Euros in this cohort, which corresponds to a saving of approximately 17,000 Euros per transplantation. This is an important factor in times, where reimbursement for hospitals is becoming more and more restrictive.

In addition to cost savings, this multicenter approach allowed evaluation of protocol minimization. Our data suggest that preoperative treatment with intravenous immunoglobulin (IVIG) and prophylactic postoperative immunoadsorption are not necessary, which has already been shown by others.[18]

In conclusion, we have established a national protocol including the reuse of specific immunoadsorption columns in ABO-incompatible kidney transplantation. The protocol and reuse of the columns proved to be efficient and safe and allowed substantial cost savings while maintaining good outcome results.

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