



ABO incompatibility in renal transplantation

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Abstract

ABO blood group incompatibility (ABO-I) was historically considered an absolute contraindication to kidney transplantation due to the significant risk of acute antibody-mediated rejection and early graft loss. Nevertheless, the urge to minimize the gap between the candidates' number on the waitlist for kidney transplants and the available kidney donors encourage investigation into finding ways to use organs from ABO-I kidney donors, especially in the era of using more potent immunosuppression therapies. This review aims to discuss a general overview of ABO-I kidney transplantation and the different protocols adopted by some transplant centers to meaningfully overcome this barrier.

Key Words: ABO incompatibility; Renal transplantation; Kidney; Transplants

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INTRODUCTION

Renal transplant is the most effective treatment for end-stage renal disease hence; there is an increasing demand for the organs available for transplantation[1]. The number of candidates on the waitlist for kidney transplants is more than 110000 and continues to grow every year[2].

Over the past few decades, the noted shortage in the kidney donor's pool compared to the growing number of candidates on the waitlist for kidney transplants made it necessary to loosen the kidney donors' acceptance criteria. The American Society of Transplantation validated the expanded criteria for kidney donation to include "marginal factors" such as donation from hypertensive and aged donors, those being historically declined by transplant centers[3]. The decision to accept expanded-criteria donors is still based on individual centers as the medical, legal, and ethical aspects remain uncertain[4].

Historically, ABO blood group incompatibility (ABO-I) was considered an absolute contraindication to transplantation due to the significant risk of acute antibody-mediated rejection (AAMR) and early graft loss[5]. Nevertheless, the urge to minimize the gap between the candidates' number on the waitlist for kidney transplants and the available kidney donors encourages investigation into finding ways to use organs from ABO-I kidney donors, especially in the era of using more potent immunosuppression therapies[6].

This review aims to discuss a general overview of ABO-I kidney transplantation and the different protocols adopted by some transplant centers to overcome this barrier.

BLOOD GROUP ANTIGENS AND KIDNEY TRANSPLANTATION

The blood group system is a collection of one or more antigens formed of sugar or protein present on the red blood cells' surface[7]. The ABO blood group antigens form four common categories (A, B, AB, and O). Those antigens are also expressed on lymphocytes, platelets, epithelial and endothelial cells[8]. Alloantibodies (isohemagglutinins) are naturally present and directed against the missing antigens (A and/or B) from the individual's RBCs. They appear in the blood at early infancy (four to six months of age as a function of intestinal colonization with bacteria)[9].

For decades, ABO blood group incompatibility has been considered a significant, if not absolute barrier for living kidney donation. Antibodies against A and/or B blood group antigens (either IgM or IgG) can cause antibody-mediated graft damage with worse outcomes related to preformed IgG antibodies[10]. Some studies reported worse outcomes in recipients with blood group O related to the predominant presence of anti A and B IgG antibodies (Abs) in those transplant recipients[10,11]. Egawa *et al*[12] reported a remarkable incidence of acute antibody-mediated rejection in recipients with blood group O who had ABO-I liver transplantation. Toki *et al*[5] studied the difference in acute antibody-mediated rejection (AAMR) rate and graft survival between 87 O-recipients and 77 other-than-O blood group recipients who underwent ABO-I kidney transplantation between 1990 and 2007. They reported a significantly higher rate of AAMR in blood group O recipients while there was no difference in graft survival.

ABO-I kidney transplantation was first reported by Hume *et al*[13] in 1955, where eight out of ten recipients experienced hyperacute rejection. Alexandre *et al*[14] discussed the first desensitization protocol in 1987 by undergoing splenectomy,

preoperative plasma exchange, and triple-drug immunosuppression (including azathioprine, corticosteroids, and antithymocyte globulin). They reported a 79% graft survival during the first year of kidney transplantation. The first procedure was performed in the United States in the mid-1990s while appeared in Europe with some delay by the early 2000s. An increasing success rate was reported with using kidneys from A2 blood group donors due to the low expression of A2 antigen on the cell membrane with an antibody titer of $\leq 1:8$ [15]. No differences in patient or graft survival were reported between the aforementioned recipients comparing those who received organs from ABO compatible (ABO-C) donors after ten years of follow-up [16]. Accepting donations from A2 and A2B donors to B recipients significantly reduce the waitlist for B recipients[17]. With the development of desensitization protocols, Tydén *et al*[18] were able to successfully perform ABO-I kidney transplantation from A1 and B donors.

Desensitization techniques

The relation between the baseline antibody titer and the long-term outcome after ABO-I kidney transplantation is still unclear. Nevertheless, some studies reported a higher risk for AAMR with higher baseline antibody titers[19]. Most centers recommend maintaining the isoagglutinin titer at levels $\leq 1:16$ during the first two weeks following ABO-I transplantation[20]. Different desensitization protocols were prescribed trying to allow for successful transplantation. The idea of desensitization depends on either removal of circulating ABO antibodies, immunomodulation, B cell population depletion, or combinations of those methods[21,22].

Removal of circulating ABO antibodies: Various methods have been used for decreasing ABO antibodies titer including plasmapheresis, immunoabsorption, double filtration plasmapheresis, and selective plasma exchange[23]. While the latter showed less adverse effects due to the preservation of essential plasma components, studies showed that single-use of selective plasma exchange was less efficient than unselective immunoabsorption in removing the circulating ABO antibodies[24]. Despite the effectiveness of the double filtration plasmapheresis to decreasing ABO antibodies titer, its use has been limited due to massive loss of coagulation factors which evidently increases bleeding risk[25].

Immunoabsorption is widely used in Europe. Some studies showed better graft survival rates compared to plasmapheresis. However, its use is limited by the availability and cost as the single session can cost about €3000[26]. Certain techniques are developed trying to lower the cost by using reusable columns for the same patient. However, this method is still not widely used in the United States[27]. Daily plasmapheresis, using 1.5 volume exchange with 5 percent albumin replacement with each plasmapheresis session, is the most commonly employed method in ABO-I transplantation in the United States to achieve the target titer $\leq 1:16$ [28]. Partial substitution with fresh frozen plasma could be used in case of abnormal coagulation profile[29].

B cell population depletion: Rituximab is a chimeric (20% rodent and 80% human) monoclonal antibody that binds to the CD20 antigen present on the cell surface and leads to depletion of mature B-cells[30,31]. It is the first approved monoclonal antibody to be used in the therapy of indolent B cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia[32]. However, the role of rituximab exceeded the clinical use in cancer patients to include various immunological disorders[33]. The vital role of rituximab expanded to include the kidney transplantation field either as induction/desensitization therapy or as a treatment of antibody-associated rejection [34].

Various studies showed no significant difference regarding patient or graft survival between rituximab and splenectomy that was historically used for desensitization in ABO-I kidney transplantation[35]. The timing and dosage of rituximab are still uncertain. A Japanese study showed that B cells were completely eliminated from the circulation by using one dose of rituximab at 15, 35, 150, or 300 mg/m² within 3 to 13 d before transplantation. Splenic B cells were not detectable after using a single dose of 35 mg/m² which is the recommended dose in various centers[36].

Despite the wide use of rituximab-based protocols, the role of B cell depletion in ABO-I kidney transplantation is still unclear. Some studies showed no patient or death-censored graft survival benefits of the inclusion of rituximab[37]. Plasma cells lack CD20 receptors and are able to produce isoagglutinin antibodies that may lead to acute antibody-mediated rejection[38]. More randomized controlled studies are needed to reach a conclusion about the efficacy, dosage, and timing of rituximab-based protocol in ABO-I kidney transplantation.

Immunomodulation: While rituximab leads to B cell population depletion, IVIG can lead to suppression of T-cell differentiation and stimulation with binding to Fc receptor of the phagocytes and B cells[39]. Moreover, IVIG is able to reduce infectious complications by replenishing the loss of IgGs. A 500 mg/kg of IVIG is recommended to be used to correct the preoperative hypogammaglobulinemia induced by plasmapheresis[40].

On the other hand, administration of high-dose IVIG may lead to hemolysis as commercial IVIG may contain anti-A and anti-B isoagglutinins. Using donor blood type or AB-negative blood type plasma that contains approximately 5 grams of immunoglobulin G per unit may be considered[41].

The role of induction therapy: With intraoperative immunosuppressive management, the rate of AAMR has been dramatically decreased, allowing ABO-I renal transplantation to be considered a successful and acceptable treatment option[2]. With waiting time for deceased donor kidneys exceeding five years in certain countries, transplanting across ABO-I broadens the donor pool and reduces the burden of donor shortage [3]. With the emergence of induction therapy, ABO-I renal transplantation now accounts for one-fourth of living donor transplantations in German centers and almost one-third of procedures in Japanese centers[6].

Induction therapy is an immunosuppressive therapy administered at the time of kidney transplantation to reduce the risk of allograft rejection[42,43]. In general, induction therapy falls into one of two categories[44]. The first relies on rabbit anti-thymocyte globulin (ATG), which is a lymphocyte-depleting polyclonal antibody. The other more common form of induction therapy utilizes interleukin 2 receptor antagonists (IL-2 RA)[44].

Previous studies have found that ABO-I kidney transplant maintained on tacrolimus, mycophenolate mofetil, and steroids have lower acute rejection rates when using ATG induction therapy compared to using basiliximab induction therapy[6].

On the other hand, other studies suggested that IL-2 RA induction therapy involving basiliximab eliminates the need for steroid maintenance therapy while providing effective induction of immunosuppression in ABO-I kidney transplant recipients[45].

Future studies would benefit from a randomized control trial comparing patients undergoing ABO-I kidney transplantation maintained on tacrolimus and receiving ATG for induction therapy to patients undergoing ABO-I kidney transplantation maintained on tacrolimus and receiving IL-2 RA for induction therapy.

The complication of ABO-I renal transplantation

Infection: ABO-I renal transplant patients have a higher risk for infectious complications due to intensified desensitization[46]. A retrospective study for 68 recipients of living kidney with 47 ABO-C *vs* 21 ABO-I showed that ABO-I has a significantly higher infection rate and longer hospitalization than the ABO-C group. Polyomavirus (BKV), cytomegalovirus (CMV), herpes simplex virus and varicella zoster virus, are the most common viral causes[6,46]. The incidence and severity of CMV infection were greater in the ABO-I group than in the ABO-C group. CMV may cause ureteric stenosis due to urethritis[46]. Zschiedrich *et al*[47] performed a single-center retrospective study on one hundred ABO-I kidney transplants, and their study showed no significant difference between ABO-I and ABO-C groups regarding infection complication and hospitalization. A meta-analysis of ABO-I renal transplant included 1,346 patients from 27 studies which reported a significant increase in severe nonviral infection (RR: 1.44, 95%CI: 1.13-1.82). CMV infection was significantly higher in ABO-I group (RR: 1.20, 95%CI: 1.04-1.37, $P = 0.01$)[6]. Infection was the cause of death in 49% of patients who were ABO-I in 49% through the first year after the transplantation compared to 13% in patients who were ABO-C[6].

Surgical complication: The ABO-I, as compared to ABO-C renal transplant patient, has a significantly higher risk for bleeding due to loss of coagulation factor during the plasmapheresis[6,47]. Unscheduled surgical intervention was higher in the ABO-I group due to increased lymphoceles[47]. Mycophenolate mofetil utilization has a statistically significant role in developing lymphocele, which should be considered during lymphocele evaluation to avoid unnecessary surgical intervention and decrease hospital length of stay[48].

Malignancy: There is no statistically significant difference in developing malignancy between ABO-I and ABO-C groups despite aggressive induction therapy[23,6,47,49].

Table 1 Literature review of studies reporting the ABO blood group incompatibility transplants, complications and outcome

| Study type | Ref. | Sample size | Desensitization/immunosuppression protocols | Complications | Success rate |
|-------------------------------------|--------------------------|---|---|--|---|
| 1 Systemic review and meta-analysis | Scurt <i>et al</i> [37] | 65063 of which 7098 undergone ABOi-rTx (ABO-incompatible renal transplantation) | Rituximab based protocols <i>vs</i> non-rituximab; splenectomy groups | Risk of bleeding; the proportion of patients with sepsis was higher after ABOi-rTx than after ABOc-rTx; no statistically significant difference was observed in the risk of UTI (D2 = 48%), CMV infection (D2 = 71%), BK polyomavirus infection (D2) | Death censored graft survival became similar to that of ABOc-rTx within the first year; compared with ABOc-rTx, ABOi-rTx was associated with significantly higher 1-yr mortality (OR: 2.17; 95%CI: 1.63-2.90), $P < 0.0001$ |
| 2 Single-center retrospective study | Lee <i>et al</i> [54] | 56 | RP group ($n = 26$) <i>vs</i> RO group ($n = 30$) | No difference in complications such as antibody-mediated rejection, biliary stricture, hepatic artery thrombosis, infection, poor graft and patient survival; biliary stricture was most common 23.1% of patients ($n = 6$) in the RP group; 16.7% in RO group ($P = 0.990$); hepatic artery thrombosis: 6.7% of patients ($n = 2$) in the RO group only; infection: 7.7% in RP group ($n = 2$) and 6.7% ($n = 2$) in the RO group, $P = 0.791$ | 6-, 12-, and 18-mo overall survival rates were 92.3%, 80.8% and 76.9% in the RP group and 96.6%, 85.4% and 85.4% in the RO group ($P = 0.5744$) |
| 3 Systemic review and meta-analysis | Lo <i>et al</i> [55] | 4810 | Immunoadsorption or apheresis; splenectomy or underwent splenectomy | From 68 studies: 878 of 2672 recipients (32.9%) experienced acute, rejections; of the above 878 recipients with biopsy-proven acute rejection episodes, there were 304 (34.6%) reported cases of acute antibody-mediated rejection, 213 (24.3%) reported cases of acute cellular rejection and 400 (45.6%) cases of undifferentiated acute rejection; 46 of 83 studies with 785 recipients reported on posttransplant infective complications. CMV is the most frequently reported infection, followed by urinary tract infections, polyomavirus, and BK nephropathy | Follow up time of 28 mo (SD: 26.6); immunoadsorption or apheresis: Graft survival 94.1% (95%CI: 88.2%-98.1%) and 88% (95%CI: 82.6%-91.8%); splenectomy or underwent splenectomy: Graft survival: 94.5% (95%CI: 91.6-96.5%) and 79.7% (95%CI: 72.9% - 85.1%) |
| 4 Single center | Tanabe <i>et al</i> [52] | 67 | Plasmapheresis and immunoadsorption to remove anti-AB antibodies prior to kidney transplantation; induction phase with methylprednisolone, cyclosporine, azathioprine, antilymphocyte globulin, and deoxyspergualin were used for immunosuppression; splenectomy at the time of kidney transplantation in all cases | 5 dies during observation.; 3 of uncontrolled bleeding due to duodenal ulcer, malignant lymphoma, cerebral hemorrhage (one each); 10 had non-tissue invasive CMV infection | Survival: 93% at 1 yr; 91% at 8 yr; graft survival 79% at 1, 2, 3 and 4 yr, 75% at 5, 6 yr, and 73% at 7 and 8 yr |
| 5 Retrospective cohort study | Okumi <i>et al</i> [53] | Study population: 1032; 555 LKT recipients (between | All of the patients were administered a triple immunosuppressive protocol comprising CNI, antimetabolite drugs, and MP; patients transplanted between 1989 and 1997 received cyclosporine and AZA, those transplanted | Significantly higher CMV rates and adenovirus infections were observed in the ABO-ILKT recipients | There were 32 graft losses among the patients who underwent ABO-ILKT before 2004 and 99 graft losses in the |

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| | | | 1989–2004), 452/555 were ABO-CLKT & 103 were ABO-ILKT; 477 LKT recipients (between 2005–2013), ABO-CLKT: 333 and ABO-ILKT: 144.; (247/1032 ABO-ILKT) | between 1998 and 2000 received TAC and AZA, and those transplanted after 2001 received TAC and MMF; after 2002, all patients received basiliximab perioperatively; splenectomies were performed at the time of transplantation between 1989 and 2004; as an alternative to splenectomy, one dose of rituximab was administered 5-7 d before transplantation | compared with the ABO-CLKT recipients before 2004. There were no differences in the frequencies between the ABO-CLKT and ABO-ILKT recipients after 2005 | ABO-CLKT group; the Kaplan-Meier cumulative graft survival rates at 9 years were 68.9% and 78.1% for the ABO-ILKT and ABO-CLKT groups, respectively, a difference that was significant (log-rank test: $P = 0.026$). After 2005, the 9-yr graft survival rates were 86.9% and 92.0% for the ABO-ILKT and ABO-CLKT groups, respectively, a difference that was not significant (log-rank test: $P = 0.279$); no particular causes of graft failure predominantly affected the ABO-CLKT or ABO-ILKT groups in either era |
| 6 | Retrospective cohort study | Takahashi <i>et al</i> [56] | 441 (Mean age 34) | Standard immunosuppressive therapy used: (1) Extracorporeal immunomodulation to remove serum A, anti-B antibodies before transplantation; (2) Pharmacotherapy (triple-drug regimen combining calcineurin inhibitor with a steroid and an antimetabolite) 66% received cyclosporin and 34% tacrolimus; (3) Splenectomy (433 of 441 patients except 8 who were children); and (4) Anticoagulation therapy (223 patients 51% received anticoagulation; 218 patients, 49% did not) | 60 patients died; 14 patients died of pneumonia; 8 of hepatic failure; 7 of heart failure; 6 of a cerebral hemorrhage; 3 with multiorgan failure with DIC; 2 patients in each: Malignant lymphoma, gastric cancer, brain tumor, gastroduodenal ulcer, acute pancreatitis, pulmonary edema, sepsis, cerebral meningitis; 1 each: Hydrocephalus, virus-associated hemophagocytic syndrome, rupture of aorta aneurysm, hemorrhage after aortic valve replacement, ileus, and suicide | Patient survival rates were 93%, 89%, 87%, 85%, and 84% at 1, 3, 5, 7, and 9 yr, respectively; corresponding graft survival rates were 84%, 80%, 71%, 65%, and 59% |
| 7 | Prospective study | Tydén <i>et al</i> [18] | 67 (mean age 34.9) | Plasmapheresis and immunoadsorption were carried out to remove the anti-AB antibodies before transplantation; induction phase: Methylprednisolone, cyclosporine, azathioprine, antilymphocyte globulin and deoxyspergualin were used for immunosuppression; local irradiation of graft of 150 rad on the 1 st , 3 rd and 5 th day after transplantation; splenectomy at the time of transplantation | 5 died during observation; 3 patients with functioning grafts died of uncontrolled bleeding due to duodenal ulcer, malignant lymphoma, and cerebral hemorrhage (one patient each); 1 patient died of ischemic colitis due to secondary amyloidosis; 1 patient of a cerebral hemorrhage after graft loss due to humoral rejection; there was no fatal infectious complication; 10 patients had a non-tissue-invasive cytomegalovirus infection | Patient survival was 93% at 1 yr and 91% at 8 yr; graft survival was 79% at 1, 2, 3, and 4 yr, 75% at 5 and 6 yr, and 73% at 7 and 8 yr; patient survival was not significantly different from that of ABO-compatible patients. Graft survival was significantly different between ABO-incompatible grafts and ABO-compatible grafts |
| 8 | Prospective observational study | Masterson <i>et al</i> [50] | Study population: 84 | Standard immunosuppression without antibody removal with steroids, mycophenolate, tacrolimus, and basiliximab; mycophenolate mofetil 500 mg, BID initiated 7-14 d pretransplant; then 1000 mg, BID as tolerated or at time of transplant then taper dose of 1500 mg/day by weeks 3-6, then 1000 mg/d by week 10-12; tacrolimus 0.05 mg/kg bid 2-3 d pretransplant, followed by 9-12 ng/mL for 2 weeks, 8-10 ng/mL weeks 3-4, 5-8 ng/mL weeks 5-24, 3-7 ng/mL weeks 25-52 and 2-4 ng/mL beyond 1 yr; Basiliximab 20 | One patient had recurrent urinary tract infections; BK viremia in four patients by screening with spontaneous resolution following a reduction in immunosuppression; no cases of CMV disease or other opportunistic infections | At 36 mo posttransplant, patient and graft survival was 100%; at 12 mo, median (IQR) serum creatinine and eGFR were 110.5 μ mol/L 77-127 and 56.5 mL/min/1.73 m ² (48-71), respectively; at 36 mo, there was no significant change in graft function with |

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|----|-----------------------------|------------------------------|--|---|---|--|
| | | | | mg days 0 and 4; prophylaxis against CMV and pneumocystis jiroveci pneumonia | | median creatinine 104 $\mu\text{mol/L}$ (82-129), eGFR 57 mL/min/1.73 m ² , and urinary albumin/creatinine ratio 2.5 mg/mmol (0.98-4.25) |
| 9 | Retrospective | Egawa <i>et al</i> [57] | 66 patients (10 mo to 55 yr old) | The basic immunosuppressive regimen consisted of tacrolimus and steroids in all groups with a target tacrolimus trough level between 10 to 15 ng/mL in the first week, 5-10 ng/mL during the first post-treatment month; methylprednisolone was administered at different doses throughout each stage; prostaglandin E1 was infused for 7 to 14 d after transplantation; cyclophosphamide was initiated 1-week pretransplant and given daily one month after transplantation, then converted to azathioprine; splenectomy was performed in all patients aged five years and older without contraindications | Incidence of intrahepatic biliary complications and hepatic necrosis in ABO-incompatible living-related grafts (18% and 8%, respectively) was significantly ($P < 0.0001$) greater than in ABO-compatible and ABO-identical grafts (both 0.6% and 0%, respectively) | Antibody titer and the clinical course followed prospectively during a period of 3 to 11 yr; 5-yr patient survival was 59%, 76%, and 80% for ABO-incompatible, ABO-compatible, and ABO-identical grafts, respectively ($P < 0.01$); in patients < 1 yr old, $> \text{or} = 1$ to < 8 , $> \text{or} = 8$ to < 16 , and $> \text{or} = 16$ yr old, 5-yr survival was 76%, 68%, 53%, and 22%, respectively |
| 10 | Retrospective study | Kimura <i>et al</i> [58] | 5549 patients (ABO matched $n = 2820$ and major incompatible $n = 1384$ and bidirectional incompatible $n = 143$) | Among the four groups of ABO compatibility, there were no significant differences in the gender distributions of patients and donors, the number of transplantations, performance status before transplantation, conditioning regimen, GVHD prophylaxis, administration of colony-stimulating factors | The cumulative incidences of transplant-related mortality differed significantly among the four groups ($P < 0.0001$), with the 1-yr rates being 27.9% (ABO-matched), 35.8% (major incompatibility), 34.2% (minor incompatibility), and 30.7% (bidirectional incompatibility) | Survival rates in the group with major and minor mismatches were significantly lower than the rate in the ABO-identical group (ABO-identical 63.0%; major mismatch, 56.9%; minor mismatch, 57.1% at one year) |
| 11 | Retrospective | Kim <i>et al</i> [59] | 89 adult patients | Acute GVHD prophylaxis consisted of cyclosporin A (CyA) + Methotrexate ($n = 57$), CYA alone ($n = 20$), CyA plus mycophenolate mofetil ($n = 11$); infection prophylaxis consisting of ciprofloxacin/metronidazole/fluconazole and acyclovir | Within the first 30 d after allogeneic PBST, bacteremia occurred in 10 (11.2%) patients, viral infections including cytomegalovirus in 20 (22.5%) patients, and fungal infections in 12 (13.5%) patients, although the incidence of infection was not statistically different between the different groups of transplantation; bleeding occurred in 3 cases; graft failure in 3 cases; toxic hepatitis 1 case | With a median follow-up duration of 13 mo (range, 0.5-61 mo); 3-yr overall survival estimates for the ABO-identical, major/bidirectional, and the minor group were 44.6 ± 9.0 , 43.1 ± 11.6 , and $43.8 \pm 13.5\%$, respectively ($P = 0.8652$) |
| 12 | Series | Montgomery <i>et al</i> [22] | 60 patients | Pre-and posttransplant PP/CMV IV immunoglobulin; quadruple, sequential immunosuppression with tacrolimus and mycophenolate mofetil. Steroids were used perioperatively. Daclizumab was used for induction; splenectomy at the time of transplant was then replaced by a single dose of anti-CD20 the night prior to transplantation | 3 patient deaths in the series; all 3 patients died with functioning grafts; cause of death included West Nile encephalitis (likely acquired from FFP transfusion). metastatic liver cancer | Patient survival at 1, 3, and 5 yr was 96.3%, 96.3%, and 89.4%, respectively; using a short course of PP and low-dose IVIG with standard maintenance immunosuppression, the death-censored graft survival of 60 consecutive ABO-I kidney transplants at 1, 3, and 5 yr was 98.3%, 92.9%, and 88.7%, respectively |
| 13 | Retrospective observational | Okada <i>et al</i> [60] | 412; ABO-I: $n = 205$ | ABO-I cases treated with Rituximab ($n = 131$); splenectomy ($n = 21$) | The incidence of infection was significantly higher in the ABO incompatible treated with Rituximab group than in the ABO-incompatible treated with neither rituximab nor splenectomy group | Graft survival for ABO-I was significantly lower than that for ABO compatible renal transplantation (92.8% vs 97.2% after five years $P = 0.0037$) |

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|----|---------------------|--------------------------|--|--|--|
| | | | | [28.2% (37/131) vs 9.4% (5/53), $P = 0.006$] | |
| 14 | Retrospective study | Rowley <i>et al</i> [61] | 158 allogeneic hematopoietic stem cell transplants from ABO-incompatible | The majority received busulfan or TBI-based conditioning regimen. 9 patients received a variety of other myeloablative conditioning regimens; 150 patients received GVHD prophylaxis consisting of cyclosporine followed by methotrexate (CSPMTX); 2 patients received MTX alone, 1 patient received cyclosporine + methotrexate, 2 patients received CSPMTX with prednisone, 3 patients received CSP and prednisone | 6 patients with suspected hemolysis due to elevated bilirubin; unable to demonstrate adverse effects from hemolysis during the first 21 d of transplantation |
| | | | The study was to demonstrate the risk of hemolysis | | |

ABOi-rTX: ABO-incompatible renal transplantation; ABOc-rTX: ABO-compatible renal transplantation; ABO-CLKT: ABO-compatible living kidney transplant; ABO-ILKT: ABO-incompatible living kidney transplant; RP: Rituximab with plasmapheresis; RO: Rituximab only without plasmapheresis; OR: Odds ratio; CMV: Cytomegalovirus; CNi: Calcineurin inhibitors; CyA: Cyclosporin; CSP: Cyclosporin A; MP: Methylprednisolone; AZA: Azathioprine; TAC: Tacrolimus; MMF: Mycophenolate mofetil; CSPMTX: Cyclosporine followed by methotrexate; GVHD: Graft versus host disease; TBI: Total body irradiation; yr: year; mo: month; FFP: Fresh frozen plasma; PP: Plasmapheresis.

Summary of literature review: There has been significant progress in desensitization protocols and optimization of ABO-I transplantation. Sufficient desensitization is possible using just rituximab, but this approach has not significantly affected patient survival. In addition, the use of immunoabsorption also appeared to be a promising preconditioning strategy as an alternative to rituximab prior to ABO-I kidney transplantation. In patients who do not undergo antibody removal prior to transplantation and use only conventional immunosuppression, it is essential to have a baseline anti-blood group antibodies (ABGAb). ABGAb titer was found to be a predictor of AbMR in ABO-I. Patients with low ABGAb titers can successfully undergo ABO-I using conventional immunosuppression alone[50]. The use of pretransplant plasmapheresis in ABO-I patients, however, was found to provide additional protection. Acute rejections, especially in kidney transplantation was found to be multifactorial. Likely due to thrombosis of the renal artery, reactive neutrophilic infiltrates and fibrin deposition at the intima, and total necrosis of the renal parenchyma[51]. The mechanism behind this was thought to occur due to the anti-A/B antibodies that would bind to renal vascular endothelial cells and activate complement, platelet aggregation, and inflammation. Starting patients on desensitization and immunosuppression protocols and in some studies, anticoagulation and prophylactic antivirals/antibiotics were found to demonstrate significant improvement in ABO-I transplantation.

ABO-I living kidney transplantation offers an excellent long-term outcome and is an acceptable treatment for end-stage renal failure[52,53]. Graft survival was almost identical over the past decade regardless of ABO-incompatibility. It has been found that the occurrence of acute rejection episodes mainly influenced the longer-term renal function in ABO-I LKT within six months and donor age (over 54 years old)[52]. Although donor age had a vital role in acute rejection, some studies have found that recipient age was also identified as a factor for outcome. As mentioned above in the chart, the studies have demonstrated, in respect to LKT with ABO-incompatibility, a substantial improvement in graft survival and decreased frequency of infectious adverse events over time. Complications, although decreasing, continue to exist, and there remains an increased risk of bleeding, infections, and organ rejection which clinicians need to be aware of as they are seen not only in ABO-I transplantation but as well as in ABOc transplantation in order to prevent further adverse effects and improve patient care. The use of preemptive antibiotics and antiviral therapy may be beneficial in these patients and close surveillance of bleeding events. Reducing the dose of immunosuppressive drugs may be beneficial, as discussed in several studies mentioned in Table 1, given the risk of infection.

CONCLUSION

ABO-I was historically considered an absolute contraindication to transplantation due to the significant risk of AAMR and early graft loss. However, the need to minimize the gap between the candidates' number on the waitlist for kidney transplants and the available kidney donors encouraged investigation into finding ways to use organs from ABO-I kidney donors, especially in the era of using more potent immunosup-

pression therapies. Desensitization protocols are used to allow ABO-I kidney transplants; these protocols include plasma exchange, B-cell depletion using rituximab, immunomodulation using IVIG. Induction of immunosuppression using ATG or IL-2 RA is required in ABO-I kidney transplants. Infections are more common with ABO-I kidney transplants compared to ABO-C kidney transplants due to more potent immunosuppression.

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