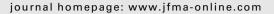


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ORIGINAL ARTICLE

B cells and immunoglobulin in ABOincompatible renal transplant patients receiving rituximab and double filtration plasmapheresis



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KEYWORDS

B cells; immunosuppressants; renal transplantation; rituximab Background/Purpose: The effect of rituximab on B cell and immunoglobulin production after therapeutic apheresis has not been studied in ABO-incompatible renal transplant patients. Methods: Twenty consecutive ABO-incompatible renal transplant patients receiving rituximab induction and double filtration plasmapheresis were enrolled; one case was excluded because of repeated plasmapheresis and immunoglobulin therapy (Incompatible group). The B cell count of the Incompatible group was compared to another group of 18 ABO-compatible renal transplant patients who were operated on during the same period (Compatible group). In the Incompatible group, the total IgM, IgG, and IgG1-4 subclasses after transplantation were compared to those before desensitization. Tacrolimus, mycophenolate mofetil, and steroids were used for both groups.

Results: The B cell count of the Incompatible group was significantly lower than the Compatible group post-transplant from Month 1 to Month 11 only. The B cell count of the Compatible group also decreased for the first 6 months, suggesting that maintenance immunosuppressive agents suppress B cells. Total IgG and IgM levels after transplantation were significantly lower than before desensitization during the 24-month follow-up period. The post-transplant IgG3 level was significantly lower than before desensitization for only 3 months.

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Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Conclusion: With the aid of tacrolimus and mycophenolate mofetil, rituximab resulted in sustained suppression of B cell count and total IgG and IgM. Among the IgG subclasses, IgG3 was less sensitive to rituximab.

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Introduction

ABO-incompatible (ABOi) renal transplantations were previously considered to be at high risk of rejection and transplant failure regardless of whether splenectomy was performed to hamper the immune response.^{1,2} Removal of anti-A/B antibodies (ABab) by therapeutic apheresis has been reported to rescue ABOi renal transplant rejection.³

With the advent of rituximab, a monoclonal anti-CD20 antibody that depletes human B cells, ABOi renal transplantations have been performed in many transplant centers with very high success rates. 4-6 Rituximab depletes B cells not only in the peripheral blood but also in the lymph nodes and transplanted kidneys. ABOi renal transplant operations are currently conducted using rituximab and various techniques of therapeutic apheresis to remove ABab. Removal or inhibition of ABab can be temporarily achieved by either plasmapheresis or immunoadsorption with or without intravenous immunoglobulin.4-6 Rebound antibody production after cessation of therapeutic apheresis has been reported in patients with autoimmune diseases as well as in those receiving immunoadsorption for ABOi renal transplantation.^{8,9} In addition, the use of rituximab after kidney transplantation has been associated with a high risk of infectious diseases and infection-related deaths. 10 However, the effects of rituximab on B cell and immunoglobulin production after therapeutic apheresis have not previously been studied in ABOi renal transplant patients.

To demonstrate the effects of rituximab on B cell and immunoglobulin production, we retrospectively reviewed the medical records of patients who had undergone ABOi renal transplantation with a preconditioning regimen including rituximab and double filtration plasmapheresis only. The immunoglobulin levels after transplantation were compared to those before desensitization, and the number of B cells of the ABOi recipients was compared to a group of ABO-compatible renal transplant patients during the same time period.

Patients and methods

Study population and design

Patients who underwent primary ABO-incompatible renal transplantation (Incompatible group) performed in a single hospital between January 2006 and December 2010 were retrospectively reviewed to assess the effects of rituximab on B cell and immunoglobulin productions. An immunosuppressive regimen including rituximab induction, double filtration plasmapheresis (DFPP) and tacrolimus-based immunosuppressive therapy was employed to bring the

ABO antibody titers down before live donor renal transplantations were performed. The numbers of B cells of the ABOi recipients were compared to a group of ABO-compatible renal transplant patients who were operated on without pretransplant rituximab and DFPP during the same time period (Compatible group). Patients with a positive crossmatch before transplantation were not included, and those who received intravenous immunoglobulin, rituximab or DFPP after transplantation because of antibody-mediated rejection were also excluded. The follow-up period was at least 12 months for all the patients.

Desensitization protocol

For ABOi renal transplantations, two doses of rituximab, which could deplete B lymphocytes but not plasma cells, were given before graft reperfusion: one dose of 200 mg about 14 days before transplantation and the other during the transplant operation. At least four sessions of DFPP were given in order to reduce the donor-specific ABab titers to 1:2. ABab titers were determined using the saline method. Briefly, two-fold serial dilutions of sera were made in saline and tested for agglutinating activity toward type A or B red blood cells.

DFPP was performed using KM-8800 in a Kuraray plasmapheresis system incorporating a Plasmacure PS-06 and an Evaflux 4A as the plasma fractionator (Kuraray Medical, Tokyo, Japan). The exchange volume was set at 50 mL/kg with normal saline 300–500 mL as the replacement fluid. Intravenous immunoglobulin was not included in the desensitization protocol but was employed to treat antibody-mediated rejection, as defined by positive C4d-staining in more than 50% of peritubular capillaries. Coagulation profiles and albumin levels were regularly checked during the pretransplant desensitization period. Frozen plasma was only given for coagulopathy, and albumin for hypoalbuminemia (<30 g/L).

Immunosuppressive therapy

Before transplantation, the patients receiving ABOi renal allografts (Incompatible group) received a 7-day preconditioning immunosuppressive therapy including tacrolimus, mycophenolate mofetil (MMF) and methylprednisolone. The initial dose of tacrolimus was 0.2 mg/day and that of MMF 1–2 g/day. The target trough level for tacrolimus was 8–12 $\mu g/L$, and the white blood cell counts were kept at more than 4 \times 10 $^9/L$ by adjusting the dose of tacrolimus and MMF. The daily dose of methylprednisolone was 40 mg/day.

Every renal transplant recipient, regardless of whether or not they were ABO-incompatible, received bolus intravenous methylprednisolone (10 mg/kg) before vascular reperfusion and a tacrolimus-based immunosuppressive

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