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ORIGINAL ARTICLE

Cytomegalovirus infection following renal transplantation in patients administered low-dose rituximab induction therapy

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Summary

Anti-CD20 antibody (rituximab) is recently being used as a B cell-depleting agent in renal transplantation (RTx). However, the incidence of infectious complications associated with rituximab therapy remains uncertain. We evaluated the incidence of cytomegalovirus (CMV) infection associated with rituximab therapy in RTx. A total of 83 patients were enrolled. The immunosuppressive regimen consisted of tacrolimus or cyclosporin, mycophenolate mofetil, methylprednisolone and basiliximab. In 54 patients, only one dose of rituximab (200 or 500 mg/kg body weight) was given before RTx. A total of 25 of 43 (58.1%) recipients who were CMV seropositive prior to RTx and who received rituximab induction therapy developed CMV infection, compared to 18 of 24 (75%) CMV seropositive recipients who did not receive rituximab therapy ($P = 0.1676$). A total of 8 of 11 patients who were CMV seronegative prior to RTx and who received rituximab developed CMV infection. However, CMV seroconversion was seen in all 8 of these infected patients. Low-dose rituximab induction therapy in renal transplant recipients appears to have no influence on the incidence of CMV infection and CMV seroconversion. However, we have to consider anti-CMV prophylaxis therapy, because of high incidents of CMV infection, especially for CMV seronegative recipients who received rituximab.

Introduction

Rituximab is a chimeric murine/human monoclonal antibody that reacts with the CD20 antigen [1]. It was first approved for use in the treatment of relapsed or refractory B cell non-Hodgkin's lymphoma [2]. Because of its selective toxicity against normal B cells, it has been used in the treatment of autoimmune diseases, i.e., autoimmune thrombocytopenic purpura, rheumatoid arthritis, systemic lupus erythematosus and autoimmune neurological disorders [3,4]. Rituximab is also being used for the treatment of post-transplant lymphoproliferative disease (PTLD) [5]. It has recently drawn attention as a tool for the treatment of rejection, prevention of rejection in ABO-incompatible transplantation, and desensitization in highly HLA-sensitized patients [6–9].

The use of rituximab has been reported to be associated with a cytokine release syndrome, late-onset neutropenia and hypogammaglobulinemia [2,10–12]. Although it might be expected that the main question while discussing the safety of rituximab would be that of the risk of infections associated with its use, there have only been a few reports of elevation in the risk of viral, bacterial or fungal infections associated with its use. In particular, it

still remains uncertain if rituximab therapy is associated with an elevated frequency and/or severity of cytomegalovirus (CMV) infection, which continues to be one of the most important complications in transplant recipients. In this study, we report on the influence of low-dose rituximab induction therapy on the incidence of CMV infection and disease in renal transplant recipients.

Material and methods

Patients

Between 2002 and 2006, kidney transplantation was carried out on 270 patients at our department. We retrospectively evaluated 83 of the 270 patients (30.7%) who underwent kidney transplantation from living donors (Table 1). Among them, 54 patients received rituximab induction therapy within 7 days prior to the transplantation (Group 1). A total of 29 living donor renal transplant recipients who underwent transplantation without rituximab therapy, but received immunosuppressive regimen consisting of tacrolimus (Tac) or cyclosporine (CsA), mycophenolate mofetil (MMF), methylprednisolone (MP) and basiliximab from October 2002 to May 2005, were enrolled as control patients (Group 2). Six of fifty-four in Group 1 and two of twenty-nine in Group 2 were second kidney transplant recipients, and 1 of 54 in Group 1 was a third kidney transplant recipient. No patient in both groups received other organ transplantation before and after kidney transplantation. All patients in Group 1 and 26 patients in Group 2 were ABO-incompatible renal transplant recipients and/or sensitized recipients. Three patients in Group 2 who were neither ABO incompatible nor sensitized were also enrolled in this cohort because these three patients received the same immunosuppressive regimen to prevent them from recurrence of their primary disease, focal segmental glomerulosclerosis.

Eleven patients in Group 1 and five patients in Group 2 were seronegative for CMV IgG prior to

Table 1. Patient demographics.

Groups	Group 1: with rituximab therapy	Group 2: without rituximab therapy	*P*
Number	54	29	NS
Age, mean ± SD (range)	41.6 ± 14.4 (14 to 64)	45.0 ± 12.9 (21 to 67)	NS
Male/female	33/21	18/11	NS
Primary disease of CRF			
Glomerulonephritis	28	12	NS
FSGS	4	3	
Dibetes melitus	3	2	
HTN	2	0	
VUR nephropathy	2	1	
PRGN	1	0	
Interstitial nephritis	1	0	
SLE	1	1	
PCKD	0	1	
MPGN	0	1	
Unknown	12	8	
CMV serostatus			
D+/R+	43	24	NS
D+/R−	11	5	
Indication of rituximab therapy			
ABOi	26	16	NS
Anti-HLA Ab positive	21	8	
ABOi + anti-HLA positive	7	2	
Dose of rituximab			
200 mg	25		
500 mg	29		
Splenectomy	8	18	$P < 0.0001$
Follow-up period, mean ± SD (months)	26.8 ± 6.2	48.4 ± 10.6	$P < 0.0001$

CRF, chronic renal failure; FSGS, focal segmental glomerulosclerosis; HTN, hypertension; RPGN, rapidly progressive glomerulonephritis; SLE, systemic lupus erythematosus; PCKD, polycystic kidney disease; MPGN, membranoproliferative glomerulonephritis; CMV, cytomegalovirus; D, donor; R, recipient; ABOi, ABO incompatibility; HLA, human leukocyte antigen; Ab, antibodies; SD, standard deviation; NS, not significant.

transplantation (CMV seronegative). All of the remaining 67 patients were seropositive for CMV IgG prior to transplantation (CMV seropositive). In addition, all of the donors were positive for CMV IgG before kidney donation.

Immunosuppressive protocol

A conventional triple-drug immunosuppressive induction protocol, consisting of Tac or CsA, MMF and MP for 1 week prior to transplantation and basiliximab (20 mg) for 2 days after transplantation, was used in all the patients (Fig. 1). All 54 patients in Group 1 also received one dose of rituximab, 2–5 days before transplantation. While 29 patients received 500 mg of rituximab, 25 received a 200 mg dose. Splenectomy was performed in 6 of the 26 ABO-incompatible recipients at the time of transplantation. Splenectomy had already been performed in one patient before transplantation. This patient was a recipient of a second transplant, and had already undergone ABO-incompatible kidney transplantation. All the ABO-incompatible recipients in Group 2 also underwent splenectomy during transplantation. All patients received three to five sessions of plasmapheresis for the removal of anti-HLA antibodies or anti-bloodtype antibodies before transplantation.

Indications for rituximab induction therapy

Rituximab induction therapy is indicated only for ABO-incompatible recipients and/or patients positive for anti-donor specific anti-HLA antibody before transplantation. Anti-HLA antibody was detected by flow cytometry and/or Luminex (One Lambda, Canogo Park, CA, USA).

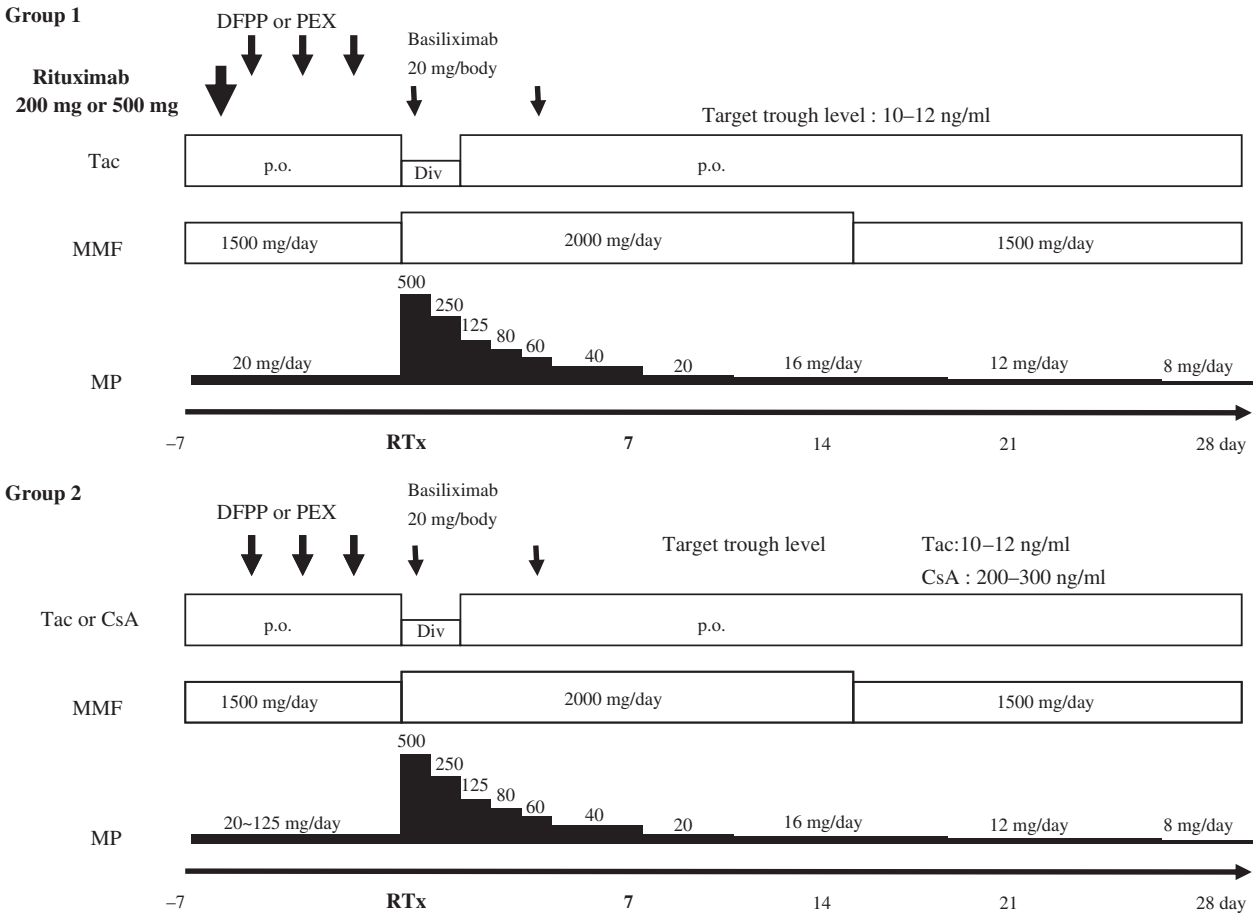

Figure 1 Immunosuppressive protocol. Plasmapheresis was performed three to five times before transplantation. Splenectomy was performed in 6 of the 26 ABO-incompatible recipients in Group 1 and all of the 18 ABO-incompatible recipients in Group 2 during transplantation. MP, methylprednisolone; Tac, tacrolimus; CsA, cyclosporine; MMF, mycophenolate mofetil; DFPP, double-filtration plasmapheresis; PEX, plasma exchange; RTx, renal transplantation.

Definition and treatment of rejection

Rejection was diagnosed by biopsy. A pathologist interpreted the biopsy slides and diagnosed the type of rejection using the Banff '07 criteria. Cellular rejections were treated with methylprednisolone (MP) 500 mg/day intravenously for 2 days, followed by a tapered regimen. When rejection was resistant to MP, it was treated with OKT3 5 mg/day for 7 days. Antibody-mediated rejection (AMR) was treated with MP pulse therapy similar to the treatment for cellular rejections, and several sessions of plasmapheresis were also performed. Only one patient in Group 1 received 200 mg of additional rituximab because the AMR of this patient was resistant to the anti-rejection therapy.

Definition of CMV infection and disease

For the purpose of this study, previously published definitions of CMV infection and disease were used [13]. Asymptomatic CMV infection was defined as the detection of CMV in blood, which was defined as the detection of CMV antigenemia in the absence of symptoms. The CMV antigen level was expressed by the total number of cells positive for the virus per 150 000 leukocytes, as determined from heparinized blood samples processed and stained with C10/C11 monoclonal antibodies, which are directed against the pp65 antigen. The CMV antigen level was assessed at weekly intervals until 3 months, 2-weekly intervals from 3 to 6 months and at monthly intervals from 6 to 12 months post-transplantation. CMV disease was defined as CMV infection accompanied by clinical manifestations. Patients with CMV antigenemia who did not fulfill the diagnostic criteria of CMV disease were not considered as CMV disease patients. The duration of CMV infection was expressed as the number of days during which the patient exhibited CMV antigenemia. If CMV antigenemia was detected again within 4 weeks of the patient becoming seronegative for CMV antigen, the interval was also included in the calculation of the duration of CMV infection.

Treatment of CMV infection

None of the patients received any prophylaxis for CMV infection. Twenty-eight of fifty-four patients in Group 1 and all patients in Group 2 who underwent kidney transplantation from 2002 to 2005 were given oral acyclovir 600 mg twice weekly for 3 months as prophylaxis therapy for herpes simplex virus ($P < 0.0001$) (Table 1). Patients with a degree of CMV antigenemia of more than 5 per 150 000 leukocytes were treated with intravenous ganciclovir at 5 mg/kg q.d. until the CMV antigenemia was no longer detected. Subjects who developed symptomatic CMV disease or who were CMV seronegative before the transplantation were administered intravenous immunoglobulin at a dose of 5 g daily for 3 days and intravenous ganciclovir at 10 mg/kg q.d. until CMV antigenemia was no longer detected, and administration of MMF was suspended in these patients until they recovered from the CMV disease. Once their CMV infection was settled, ganciclovir therapy was suspended and anti-CMV infection therapy was not resumed until their CMV antigen level increased to more than 5 per 150 000 leukocytes again.

CMV seroconversion

Cytomegalovirus seroconversion in CMV seronegative recipients was defined as the detection of CMV IgM. CMV IgG and IgM were measured by enzyme-linked immunosorbent assay (ELISA). Examination for both was conducted two to eight times until the recipients became positive for CMV antibodies.

Statistical analysis

Various parameters, including gender, age, CMV serostatus, splenectomy, follow-up period, acute rejection episodes, and CMV infection and disease episodes, in both CMV seropositive and seronegative recipients were analyzed and compared between the two groups. The relationship between the incidence of CMV infection and the dose of rituximab was also analyzed. Statistical analysis was performed using the two-way *t*-test for categorical variables, and Mann–Whitney's *U*-test for continuous variables. Multivariate association between CMV infection and predictor variables, consisting of age, gender, follow-up period, rituximab induction, CMV serostatus before transplantation, acute rejection, ABO incompatibility, splenectomy and acyclovir prophylaxis, was measured with hazard ratio (HR). Logistic regression was used to examine the associations between predictor variables and CMV infection. The log likelihood ratio was used to assess the significance of the association fitted in this model. Significance of the individual regression estimates was tested by Wald statistics. All statistical analyses were performed using SAS version 5.0. The significance level was set at 0.05 for all tests.

Results

Patient characteristics

The distributions of gender, age and CMV serostatus were similar in the two groups (Table 1). Splenectomy was highly performed in Group 2 (18/29; 62.1%) in

comparison with Group 1 (8/54; 14.8%); $P < 0.0001$. Median follow-up period of Group 2 (48.4 ± 10.6 months) was significantly longer than that of Group 1 (26.8 ± 6.2 months); $P < 0.0001$. One graft loss occurred within 1 year of transplantation in Group 1. No graft loss was observed in Group 2. The acute rejection rate was significantly higher in Group 2 (12/29; 41.1%) than in Group 1 (12/54; 18.5%); $P = 0.0245$ (Fig. 2). No patient in Group1 was treated with OKT3, while two patients in Group 2 required OKT3 therapy for steroid-resistant acute rejection ($P = 0.0508$). These two patients were positive for CMV infection after OKT3 therapy ($P = 0.3473$). None of the patients developed life-threatening infectious disease including PTLD except for CMV disease.

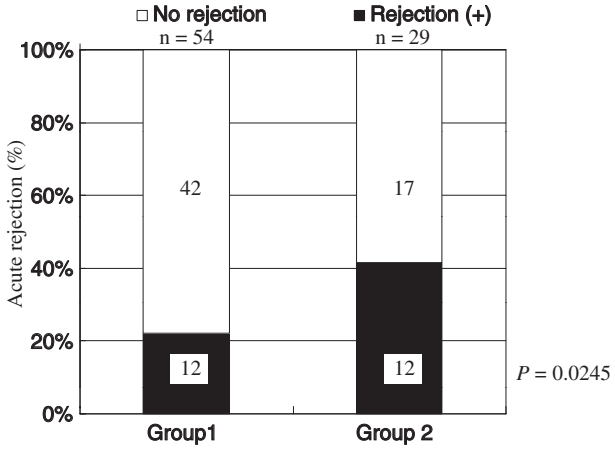

Figure 2 The percentage of acute rejection in both groups. The rate of acute rejection in Group 2 was significantly higher than that in Group 1 ($P = 0.0245$). In Group 1, 4 of 12 events were antibody-mediated rejection (AMR), 5 of 12 were cellular rejection (CR) and 3 of 12 were both AMR and CR. In Group 2, 6 of 12 rejection events were AMR, whereas 6 of 12 were CR.

Risk factors for CMV infection

The multivariable model did not reveal a significant association between CMV infection and rituximab induction therapy (HR = 1.360 (95% Confidence interval (CI): 0.181–10.206) $P = 0.7651$) (Table 2). Significant relationship with CMV infection was only noted for acute rejection (HR = 6.396 (95% CI: 1.415–28.901) $P = 0.0074$) and CMV serostatus before transplantation (HR = 5.154 (95% CI: 0.971–27.027) $P = 0.0382$).

CMV infection and disease in CMV seropositive recipients

Twenty-five of the 43 (58.1%) CMV seropositive recipients in Group 1 suffered from CMV infection, as compared to 18 of the 24 seropositive patients (75.0%) in Group 2 ($P = 0.1676$). None of the patients was diagnosed as having CMV disease in either group. None of the CMV seropositive recipients in Group 1 showed negative seroconversion after rituximab induction therapy. We also evaluated CMV IgG titer and peripheral CD19-positive B lymphocyte before and after transplantation in CMV seropositive recipients. There was no difference between CMV IgG titer before rituximab induction and that at 3–6 months after rituximab induction (from 99 ± 159.5 to 108.5 ± 128.3 IU, $P = 0.7172$), whereas the ratio of peripheral CD19-positive B cell in whole white blood cells remained suppressed at 3–6 months after transplantation (from 11.8 ± 6.7 to 1.0 ± 0.7 %, $P < 0.0001$).

Relationship between the dose of rituximab and the incidence of CMV infection

Eighteen of the 29 (62.1%) recipients who received 500 mg of rituximab, including 6 of the 11 CMV seronegative recipients, developed CMV infection, as

Table 2. Hazard ratio of CMV infection for variables included in the multivariable Cox model.

	Hazard ratio	95% CI	*P*
Rituximab (referent: no rituximab)	1.360	0.181–10.206	0.7651
Age	0.963	0.923–1.005	0.0735
Male (referent: female)	0.840	0.277–2.552	0.7585
Follow-up period	0.952	0.868–1.044	0.2884
CMV IgG negative (referent: CMV IgG positive)	5.154	0.971–27.027	0.0382
Acute rejection (referent: no acute rejection)	6.396	1.415–28.901	0.0074
ABO incompatibility (referent: ABO compatible)	1.576	0.432–5.751	0.4910
Splenectomy (referent: no splenectomy)	1.321	0.245–7.135	0.7452
Acyclovir (referent: no acyclovir)	0.451	0.089–2.274	0.3297

CMV, cytomegalovirus; CI, confidence interval.
Shown for all continuous variables are hazard ratios (95% CIs) associated with a 1 SD higher level of the variables.

Table 3. Demographics of CMV seronegative recipients.

Patients	Dose of rituximab	CMV infection	CMV disease	Type of CMV disease	Period of CMV infection	CMV sero-conversion	Period from infection to seroconversion	CMV IgG titer after seroconversion	Rejection	Banff '07 classifi-cation
Group 1										
Male, 28 years	500 mg	+	+	CMV syndrome	88 days	+	37 days	11 IU	+	1A
Female, 33years	200 mg	+	+	CMV syndrome	158 days	+	37 days	7 IU	–	–
Male, 22 years	200 mg	–	–	–	–	–	–	–	–	–
Female,14 years	200 mg	+	–	–	160 days	+	92 days	3 IU	–	–
Female, 29years	500 mg	+	+	CMV syndrome	172 days	+	96 days	9 IU	–	–
Female, 30 years	500 mg	+	–	–	169 days	+	Unknown	11 IU	–	–
Female, 37 years	200 mg	+	–	–	128 days	+	96 days	14 IU	–	–
Female, 25 years	500 mg	–	–	–	–	–	–	–	–	–
Male, 59 years	500 mg	+	–	–	60 days	+	Unknown	6 IU	–	–
Male, 19 years	200 mg	–	–	–	–	–	–	–	–	–
Female, 21 years	500 mg	+	–	–	292 days	+	38 days	5 IU	–	–
Group 2										
Male, 31 years	–	+	+	CMV syndrome	246 days	+	29 days	21 IU	+	1A
Female, 56 years	–	+	+	CMV syndrome	158 days	+	Unknown	63 IU	+	1A
Male, 24 years	–	+	–	–	174 days	+	19 days	20 IU	–	–
Male, 49 years	–	+	+	CMV syndrome	128 days	Unknown	Unknown	ND	–	–
Female, 31 years	–	+	+	CMV syndrome	98 days	+	35 days	6 IU	–	–

ND, not done.

compared to fifteen of 25 (62.5%) recipients, including 5 of the 11 CMV seronegative recipients who received 200 mg of rituximab ($P = 0.8764$). We also compared the rate of infection in Group 1 patients receiving acyclovir prophylaxis therapy. However, there was no difference between patients who received 200 mg or 500 mg of rituximab ($P > 0.9999$).

CMV infection and disease in CMV seronegative recipients

Eleven of the 54 patients in Group 1and five of Group 2 were seronegative for CMV antibody before transplantation, as described above (Table 3). Eight of the 11 recipients developed CMV infection, and 3 of these 8 infected recipients developed CMV disease, while all five patients in Group 2 developed CMV infection ($P = 0.1951$) and four of them developed CMV disease ($P = 0.0488$). Ganciclovir therapy could not be administered before the onset of CMV disease, because the CMV antigenemia of the patients did not increase more than 5 per 150 000 leukocytes until they developed CMV disease. The type of CMV disease in both groups was CMV syndrome, and there were no patients with end-organ CMV disease. The duration of CMV infection in Group 1 was not longer than that in Group 2 (Group 1: 153.4 ± 69.2 days, $n = 8$. Group2: 160.8 ± 55.8 days, $n = 5$; $P = 0.7697$). The infection could be controlled by anti-CMV therapy in all cases, and all of the patients receiving rituximab who developed CMV infection acquired anti-CMV antibody during the anti-CMV treatment.

Discussion

Since Alexandre *et al.*[14] reported the first ABO-incompatible kidney transplantation in 1987, splenectomy has been performed as a part of preconditioning therapy. However, splenectomy can lead to complications, including postoperative hemorrhage, pancreatic injury, leakage of pancreatic juices and can also increase the risk of infections, especially in small infants. While some studies have shown the benefits of rituximab therapy as a substitute for splenectomy [6,7], the effect of rituximab therapy administered with other immunosuppressive drugs on the infectious morbidity and mortality is still unknown.

Life-threatening CMV diseases and increased risk of CMV infection have been reported following rituximab administration for hematologic malignancy, meanwhile some reports have showed lower incidents of CMV infection in transplantation with rituximab [6,15–17]. Some studies also reported increased risk of T cell-mediated infections including pneumocystis jiroveci in rituximab treated patients, with agents that affect cellular immunity [18,19]. However, the doses of rituximab and the kinds of immunosuppressive agents given with rituximab were not consistent in these studies, it was not determined whether rituximab induction therapy had influence on CMV infection and other T cell-mediated infections.

Japan has an extreme shortage of cadaveric kidneys. To ensure a supply of donor kidneys, more than 500 cases of ABO-incompatible living kidney transplantation have been performed since 1989 [20]. We started to use rituximab induction therapy for ABO-incompatible kidney transplantation and have used this drug in 60 patients since 2005. In this study, we evaluated the influence of rituximab induction therapy on the incidence of CMV infection and disease, the relationship between the incidence of CMV infection and the dose of rituximab, and the incidence of CMV seroconversion in CMV seronegative patients receiving kidneys from CMV seropositive donors.

In our study, we found no significant differences in the frequency of CMV infection or disease between patients receiving rituximab induction therapy and those who did not. Rituximab reacts with the CD20 antigen expressed on pre-B and mature B lymphocytes. Three different mechanisms have been proposed for the elimination of B cells by rituximab, namely, complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and stimulation of the apoptotic pathway [1,10]. ADCC at the level of the effector cells (i.e. natural killer cells and macrophages) is considered to play a main role in the clinical effects of rituximab. We speculated on three reasons as to why we could not detect any significant differences in the incidence of CMV infection between the two groups. The first reason is the existence of plasma cells and B cells which do not express CD20. The antigen is not expressed on stem cells, pro-B cells or plasma cells; therefore, rituximab does not affect these cells, especially mature plasma cells, after transmigration to the bone marrow [21]. Actually, we did not detect any significant differences in the serum IgG levels before and after rituximab therapy, and the CMV IgG titers did not change after rituximab administration (date not shown). The second reason is that rituximab does not impair T cell immune responses [22]. Co-stimulation by T lymphocytes also plays an important role in inducing CMV IgG. CD8+ T lymphocytes and natural killer cells are not affected by rituximab, and they may also be important for the prevention of viral infections. The third reason is the existence of CD27+ memory B cells in the spleen after rituximab therapy. While Sidner *et al.* [23] demonstrated depletion of CD19+ CD27+ memory B cells in the peripheral blood, Ramos *et al.* [24] showed that rituximab did not reduce the number of CD27 + memory B cells in the spleen. These CD27+ memory B cells may also play a role in protection against CMV infection.

We used both 200 and 500 mg of rituximab for the induction therapy in this study. We did not find any significant differences in the incidence of CMV infection between the patients receiving the two doses. There is a report of fatal reactivation of CMV in a transplant patient with PTLD who died despite treatment with ganciclovir [25]. This patient received 4-weekly courses of rituximab (375 mg per square meter body-surface area). We determined the dose of rituximab by counting the number of CD19-positive B cells in the spleens removed during transplantation in patients receiving rituximab induction therapy (not published). We confirmed that CD19-positive cells no longer existed in the spleen of patients who received more than 200 mg of rituximab. As our purpose was not to remove a large number of malignant B lymphocytes, it would seem that the dose of rituximab should be minimized to protect recipients from various infectious diseases after transplantation.

Despite some studies having shown that rituximab inhibits primary and secondary humoral immune responses [26–28], we confirmed CMV seroconversion in four recipients who had received rituximab therapy and were CMV seronegative before transplantation. Peripheral CD19-positive B lymphocytes were still depleted in all the recipients administered rituximab therapy who showed CMV seroconversion. Sidner *et al.* demonstrated that CD19+ CD5+ B cells, which seem committed to the production of polyreactive natural antibodies, begin to recover earlier than CD19+ CD27+ B cells [23]. It was confirmed that the CD19+ CD5+ B cell subset begins to increase by 6 months post-transplantation. We consider that the CD19+ CD5+ B cells played an important role in the CMV seroconversion, because the time of CMV seroconversion coincided with that of the appearance of the CD19+ CD5+ B cells. Sidner *et al.* did not examine the CD19+ CD5+ B cell count between 3 and 6 months after rituximab therapy in their study. Therefore, it is possible that the recovery of CD19+ CD5+ B cells may occur even a little earlier than 6 months. When the CD19+ CD5+ B cells recover, they may start producing anti-CMV antibody. Moreover, Hamaguchi *et al.* [29] demonstrated that the peritoneal cavity provides a protective niche for CD19+ CD5+ B1 cells during anti-CD20 immunotherapy in mice. In our study, it took no less than 4 months after rituximab induction therapy for the CMV antibodies to appear.

In addition, refractory and prolonged CMV infection was not seen in any of the CMV seronegative recipients who received rituximab therapy. This might suggest that the T cell responses which are not affected by rituximab therapy and some mature memory B cells and antibody-producing plasma cells which do not express CD20 may play important roles in the protection against CMV infection in patients receiving rituximab therapy.

In this study, we performed pre-emptive therapy for CMV infection; however, we observed 56 of 83 (67.5%) patients developing CMV infection, and we especially

confirmed that 7 of 16 (43.8%) CMV seronegative recipients developed CMV disease. CMV remains one of the most important post-transplant viral pathogens despite the availability of effective antiviral drugs and validated strategies for therapeutic intervention [30]. CMV infection has been implicated in the development of both acute and chronic rejection and has been associated with decreased allograft and patient survival [31]. High incidence of CMV infection and CMV disease in this cohort may lead to poor graft and patient survival. On the other hand, universal prophylaxis with valganciclovir or oral ganciclovir is now the preferred strategy for high-risk CMV D+/R− solid organ transplant recipients. Prophylaxis significantly reduced CMV replication over preemptive treatment (6% vs. 59%) during the first 100 days in a recent randomized controlled trial of kidney transplantation [32], and the efficacy of valganciclovir for prophylaxis of CMV reactivation in patients receiving alemtuzumab, which is a humanized monoclonal antibody targeting the CD52 antigen presented on both B cells and T cells, was also confirmed [33]. In Japan, we could not induce prophylaxis therapy by either ganciclovir or valganciclovir, because Japanese health insurance system has not covered anti-CMV prophylaxis therapy even in high-risk recipients, such as CMV D+/R− cases and recipients induced T-cell-depleting agents. We should evaluate not only the efficacy of the prophylaxis therapy but also the length and the dose of prophylactic agents in kidney transplantation with low-dose rituximab induction therapy in future.

In conclusion, this study indicates that administration of a single low dose of rituximab in patients undergoing renal transplantation does not have any influence on the incidence of CMV infection, either in CMV seropositive or in CMV seronegative recipients. However, as this study was based on a small number of subjects and also short-term evaluation, the results must be confirmed by studying a larger number of patients followed up for longer periods of time.

Authorship

HN, HI, KT: designed this study. HN, HI, TT, HA, KO, HS, TS, SI, DT, YY, KT: performed this study. HN: collected and analyzed data, and wrote this paper.

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