Hindawi Publishing Corporation
ISRN Transplantation
Volume 2013, Article ID 819025, 8 pages
http://dx.doi.org/10.5402/2013/819025

Research Article

Effects of Rituximab on the Development of Viral and Fungal Infections in Renal Transplant Recipients

Samir J. Patel,[1] Jennifer M. Devos,[1] Richard J. Knight,[2] Kyle L. Dawson,[1] Wadi N. Suki,[3] Juan M. Gonzalez,[3] Abdul A. Abdellatif,[4] and A. Osama Gaber[2]

[1] *Department of Pharmacy, Houston Methodist Hospital, 6565 Fannin Street, DB1-09, Houston, TX 77030, USA*
[2] *Department of Surgery, Houston Methodist Hospital, 6550 Fannin Street, SM1661, Houston, TX 77030, USA*
[3] *Department of Nephrology, Houston Methodist Hospital, 6550 Fannin Street, Suite 1001, Houston, TX 77030, USA*
[4] *Department of Nephrology, Baylor College of Medicine, 1709 Dryden Street, Houston, TX 77030, USA*

Correspondence should be addressed to Samir J. Patel; spatel2@tmhs.org

Received 19 August 2013; Accepted 8 September 2013

Academic Editors: P. Ditonno and M. Veroux

Background. Rituximab is becoming increasingly utilized in renal transplant recipients; however, its association with infections remains unclear. *Methods*. We reviewed the incidence of viral and fungal infections in kidney transplant recipients treated with ($n = 55$) or without ($n = 386$) rituximab (RTX) in addition to standard immunosuppression. *Results*. Infections occurred in 134 (30%) patients, with a greater proportion in RTX versus no RTX patients (47% versus 28%; $P = 0.005$). Viral infections occurred in 44% and 27% of RTX and no RTX patients, respectively ($P = 0.012$). This was largely driven by the frequency of BK viremia and noncytomegalovirus/non-BK viruses in RTX patients (27% versus 13% ($P = 0.011$) and 15% versus 2% ($P < 0.001$), resp.). Fungal infections also occurred more often in RTX patients (11% versus 3 %; $P = 0.009$). Multivariate analysis revealed deceased donor recipient (odds ratio = 2.5; $P < 0.001$) and rituximab exposure (odds ratio = 2.2; $P = 0.016$) as independent risk factors for infection. Older patients, deceased donor recipients, those on dialysis longer, and those with delayed graft function tended to be at a greater risk for infections following rituximab. *Conclusions*. Rituximab is associated with an increased incidence of viral and fungal infections in kidney transplantation. Additional preventative measures and/or monitoring infectious complications may be warranted in those receiving rituximab.

1. Introduction

The anti-CD20 monoclonal antibody rituximab (RTX) has become a more widely utilized therapy in the renal transplant population. RTX use has expanded from treatment of posttransplant lymphoproliferative disease to facilitation of ABO-incompatible transplantation, reduction of human leukocyte antigen (HLA) antibodies in highly sensitized patients, treatment of antibody mediated rejection (AMR), and treatment of recurrent and *de novo* renal diseases [1–4]. Each of these conditions represents a significant challenge in renal transplantation by which B-cell depletion with RTX may represent a promising intervention.

It is well known that, with more potent immune suppression, the risk of infectious complications after transplant increases. T-lymphocyte depleting preparations in particular have been associated with an increased risk, as opposed to nonlymphocyte depleting agents which demonstrated similar infectious risks when compared to placebo [5, 6]. RTX has generally been considered to have an acceptable safety profile in hematological and autoimmune disorders; however, whether it can be used without an increased risk of infectious complications remains controversial in the immunosuppressed population [3, 7–14].

The purpose of the current study was to compare the incidence and type of viral and fungal infections in a consecutive group of kidney transplant patients receiving RTX in addition to standard immunosuppressive therapies to patients not exposed to RTX. Risk factors and time to develop infection are also examined. This study characterizes

a large series of patients receiving a similar maintenance immunosuppression, a uniform prophylaxis regimen, and routine posttransplant screening for BK and cytomegalovirus (CMV) replication.

2. Materials and Methods

This was a retrospective, observational study of consecutive adult kidney-alone and combined kidney-pancreas recipients transplanted at a single center between January 2007 and July 2010. Patients experiencing graft loss in the first month and subjects who did not receive antibody induction therapies perioperatively were excluded. The study was approved by The Methodist Hospital Institutional Review Board.

Choice of antibody induction was determined by the center's immunologic risk-based protocol. Low-risk patients, defined as non-African American patients with panel reactive antibody (PRA) less than 20%, received interleukin-2 receptor antagonist (IL2ra) therapy with either daclizumab (Zenapax, Roche, Nutley, NJ, USA) 2 mg/kg IV or basiliximab (Simulect, Novartis, East Hanover, NJ, USA) 20 mg IV, on post-operative days 0 and 3; high-risk patients, defined as African Americans, patients with PRA>20%, repeat transplants, and combined kidney-pancreas recipients, received anti-thymocyte globulin [ATG; (Thymoglobulin, Genzyme, Boston, MA)] 1.5 mg/kg/dose for 3–5 doses beginning intraoperatively. Dosages were adjusted in accordance with the product's prescribing information [15]. Patients with HLA antibodies against their donor received perioperative RTX (Rituxan, Genentech, San Francisco, CA, USA) as a part of a desensitization strategy in conjunction with ATG induction. When used for desensitization, RTX was administered as a 1000 mg dose. Patients with a historical positive cytotoxic crossmatch due to donor specific antibodies (DSA) also received IV immunoglobulin (IVIG) and therapeutic plasmapheresis in addition to RTX. Due to the long half-life and pharmacodynamic effects in patients with end stage renal disease [16, 17], patients receiving RTX for desensitization prior to transplantation were also included in this study. Indications for posttransplant administration of antibodies included biopsy-proven cellular rejection (Banff score > 1a) for ATG, and AMR, DSA development, and glomerulopathies for RTX.

Maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil, and prednisone. IV methylprednisolone was given intraoperatively and tapered to an oral prednisone dosage of 5–10 mg daily by POD 60. Mycophenolate mofetil was administered at a goal dose of 2 grams/day. Tacrolimus trough levels were maintained at 8–12 ng/mL for the first 6 months and 5–10 ng/mL thereafter.

Infection prophylaxis was administered following transplantation and treatment of rejections. This included clotrimazole four times daily for 1 month, sulfamethoxazole-trimethoprim single strength daily (or inhaled pentamidine for sulfa-allergic patients) for 6–12 months, and valcyte 450 mg daily for 3 months in nonhigh risk CMV transplants, and 6 months in high-risk (i.e., D+/R−) recipients. Pancreas recipients received 1 month of fluconazole 200 mg daily instead of clotrimazole following transplantation. Routine CMV and BK polymerase chain reaction (PCR) screening was employed at 1, 3, 6, 9, and 12 months and then every 6 months after transplant and whenever clinically warranted.

The primary endpoint of the study was the incidence of viral and fungal infections among RTX-treated patients (RTX group) compared to patients not exposed to RTX (no RTX). Only infectious complications occurring after the antibody exposure were included in the analysis. The following infections were included in the analysis: (1) CMV infection: defined as a detectable viral load in plasma (>300 copies/mL) measured by PCR and/or viral inclusions on histopathologic specimens, in combination with compatible symptoms; (2) BK virus infection: defined as detectable BK viral DNA in plasma (>750 copies/mL) in two consecutive measurements. All BK-viremic patients underwent protocol biopsy for presence of nephropathy; (3) "other" viral infections: defined as viral infections other than CMV or BK diagnosed by serologic testing, quantitative viral load measurements, and histopathologic assessment in conjunction with attributable signs and symptoms; and (4) fungal infections: defined as any positive fungal culture or staining of biopsy material, excluding oral candidiasis. Secondary endpoints included the incidence and types of specific infections, time to infection, and subgroup analyses based on IVIG administration and retransplantation status.

Continuous variables including recipient age, peak PRA, cumulative ATG dosages, and total number of infections per patient were compared using Student's t-tests. Gender, race, presence of diabetes, donor type, history of prior transplant, high-risk CMV status, immunosuppressive type, and incidence of infections were compared using chi-squared or Fisher's exact test. Due to the difference in sample sizes, categorical variables listed in Tables Tables 1–3 are shown as % (n). A univariate analysis of risk factors for infection was performed, and those factors with a P value of less than 0.2 were included in a nominal logistic multivariate analysis. Statistical analysis was performed using JMP version 7.0 (SAS Institute, Cary, NC, USA).

3. Results

A total of 453 kidney-only or kidney-pancreas transplants were performed during the study period. Seven patients were excluded for not receiving the antibody therapies at the time of transplantation, and 5 were excluded for graft loss within the first month. Characteristics of the remaining 441 patients included a mean age of 48 ± 14 years, 59% male, 61% deceased donor, and 43% Caucasian. Diabetes (30%) and hypertension (23%) were the leading causes of end stage renal disease. Fifty-five patients comprised the RTX group. Median followup for the entire cohort was 31 months (range from 3 to 56), with no difference in mean followup between groups. Major differences between the groups were driven by our desensitization protocol in which there was a predominance of Caucasian living donor transplant recipients, highly sensitized patients, and patients receiving a repeat transplant (Table 1).

Table 1: Demographics and transplant characteristics.

Variable	RTX $n = 55$	No RTX $n = 386$	P value
Age, years	47 ± 14	49 ± 14	0.42
Race			
Caucasian, % (n)	65 (36)	40 (155)	<0.001
African American, % (n)	18 (10)	27 (104)	0.15
Male gender, % (n)	42 (23)	61 (235)	0.008
Diabetes history, % (n)	24 (13)	36 (137)	0.08
Concurrent viral disease[a] % (n)	4 (2)	6 (24)	0.42
Peak PRA, %	53 ± 41	20 ± 31	<0.001
Deceased donor, % (n)	45 (25)	38 (145)	0.26
Retransplant, % (n)	24 (13)	7 (27)	<0.001
Pretransplant dialysis, years	3.2 ± 4	2.7 ± 3	0.27
Kidney-pancreas recipient, % (n)	9 (5)	7 (26)	0.54
CMV donor+/recipient− serostatus	22 (12)	17 (67)	0.43
Delayed graft function	9 (5)	9 (36)	0.97

Abbreviations—PRA: panel reactive antibodies; CMV: cytomegalovirus.
[a]Concurrent viral disease includes history of hepatitis B, hepatitis C, or human Immunodeficiency virus.

Table 2: Baseline and posttransplant immunosuppression.

Variable	RTX $n = 55$	No RTX $n = 386$	P value
IL2ra induction, % (n)	18 (10)	40 (156)	<0.001
Perioperative ATG, % (n)	84 (46)	63 (242)	0.001
Perioperative IVIG, % (n)	33 (18)	2 (5)	<0.001
Tacrolimus at discharge, % (n)	100 (55)	100 (386)	
Mycophenolate at discharge, % (n)	100 (55)	100 (386)	
Prednisone withdrawal, % (n)	5 (3)	13 (51)	0.07
Acute rejection, % (n)	51 (28)	15 (56)	<0.001
Antibody-mediated rejection, % (n)	23 (12)	3 (11)	<0.001
ATG for rejection, % (n)	29 (16)	7 (28)	<0.001
Total ATG exposure, (mg/kg)	8.5 ± 6.5	5.7 ± 2.4	<0.001

Abbreviations—IL2ra: interleukin-2 receptor antagonist; ATG: antithymocyte globulin; IVIG: intravenous immune globulin.
[a]Concurrent viral disease includes history of hepatitis B, hepatitis C, or human Immunodeficiency virus.

A significantly greater percentage of RTX patients received perioperative IVIG and/or ATG as a result of their higher immunologic profile (Table 1). There were no differences in tacrolimus trough levels, mycophenolate dosages, or prednisone dosages throughout the study period (data not shown). Rejection episodes, including those requiring treatment with ATG, occurred more frequently in the RTX group, and RTX patients received significantly more ATG post-transplant (Table 2).

A total of 64 RTX doses were administered to the 55 RTX patients. Indications included desensitization of a living donor recipient ($n = 18$), rejection ($n = 16$), desensitization of a deceased donor recipient ($n = 15$), DSA formation ($n = 8$), and recurrence of a glomerulopathy ($n = 7$). Nine patients received a second dose of RTX, and none received more than two. Recurrent diseases for which RTX was administered included focal segmental glomerulosclerosis ($n = 3$), membranoproliferative glomerulonephritis ($n = 2$), Wegener's granulomatosis ($n = 1$), and membranous nephropathy ($n = 1$). RTX was administered at a median dose of 1000 mg (range from 200 to 1000 mg) or 550 mg/m^2 per dose based on the average body surface area of the cohort. Depending on indication, some RTX dosages were administered concomitantly with additional therapies including ATG (58%), IVIG (47%), and plasmapheresis (23%). All patients receiving plasmapheresis were also administered IVIG. In addition, 2 RTX-treated patients received bortezomib as part of an antirejection regimen. The median and mean times from transplantation to first dose were 2 days (range from −265 to 827) and 99 ± 214 days, respectively.

At least one infection occurred in 134 (30%) of the 441 patients, at a median of 5.1 (range 0.4 to 28.5) months after

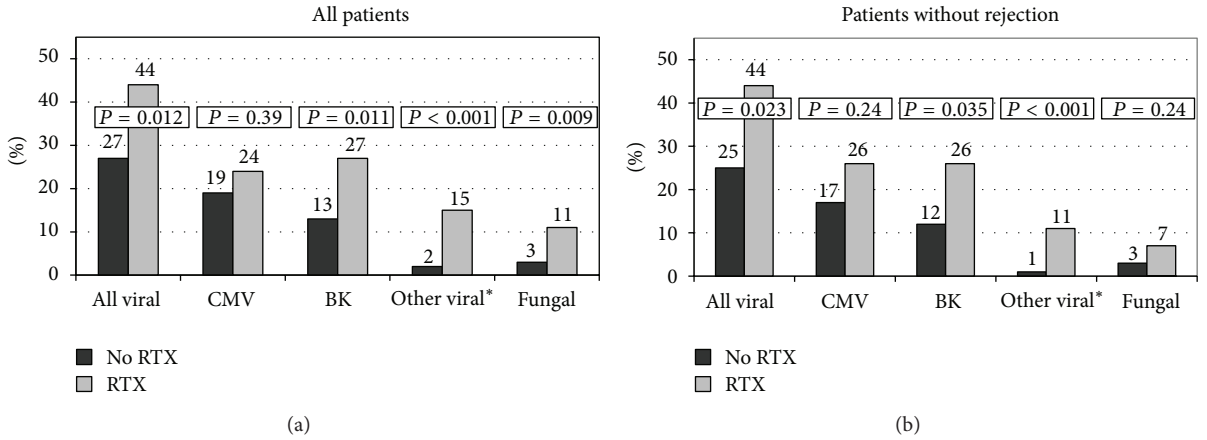

Figure 1: (a) Incidence of viral and fungal infections according to rituximab exposure in the entire cohort. (b) Incidence of viral and fungal infections, excluding patients treated for acute rejection. *represents all viral infections except for cytomegalovirus and BK.

antibody exposure. The combined incidence of viral and fungal infections was significantly higher in the RTX group than in the no RTX group (47% versus 28%; $P = 0.005$). Viral infections occurred more frequently in the RTX group compared to the no RTX group (44% versus 27%; $P = 0.012$), owing primarily to a higher rate of BK virus and other non-CMV/non-BK viral infections (Figure 1(a)). Similarly, fungal infections occurred more frequently in the RTX group (11% versus 3%; $P = 0.008$). To determine the rate of infections in patients who did not require additional antirejection therapies, we reviewed the incidence of infections between groups after excluding all patients with rejection (Figure 1(b)). This resulted in findings similar to those seen in the entire cohort.

Specific types of viral and fungal infections by group are shown in Table 3. As previously mentioned, the rate of overall viral infections seen in the RTX group was largely driven by the significantly higher rate of BK viremia and non-CMV/non-BK viruses as compared to the no RTX group (27% versus 13% and 15% versus 2%, resp.; $P < 0.01$). BK nephropathy was diagnosed in 15% of RTX-treated patients compared 4% in the no RTX group ($P < 0.001$). There was no difference in the rate of CMV between groups. As shown in Figure 2, most cases of CMV and BK in RTX-treated patients occurred in the first 6 months after antibody exposure, whereas a number of "other" viral and fungal infections occurred after 6 months.

The most common non-CMV/non-BK viral infection was varicella zoster infection, which occurred in 4 RTX patients and 1 no RTX patient. Three RTX patients with viral infections died. These included one case of EBV-associated PTLD (occurring after RTX administration) in a living donor recipient with DSAs, a patient with respiratory syncytial virus (RSV) after receiving RTX for a rejection episode following a second transplant, and a third recipient who developed JC virus-associated progressive multifocal leukoencephalopathy (PML), approximately 30 months after receiving two doses of RTX for a severe renal and pancreas allograft rejection.

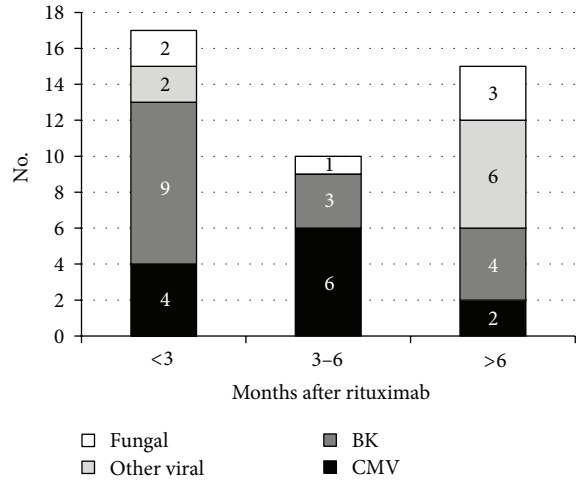

Figure 2: Timeline of viral and fungal infections after rituximab. Other viral infections: <3 months: RSV (1) and EBV (1); >6 months: varicella zoster (4), influenza H1N1 (1), and JC Virus (1). Fungal infections: <3 months: candida glabrata urinary tract infection (1), and disseminated tinea corpis (1); 3–6 months: candida esophagitis; >6 months (1): candida esophagitis, candidemia (1), nonaspergillus mould pneumonia (1), candidal brain abscess (1).

Fungal infections were more frequent in the RTX group. Of note, several severe fungal infections occurred in the no RTX group, including cases of pulmonary aspergillus (4), cryptococcal meningitis (3), mucormycosis (1), gastrointestinal invasive candidiasis (1), and candidal brain abscess (1). One patient with HCV had concurrent aspergillus and cryptococcal infections. Each patient with aspergillus and/or cryptococcal infection was treated successfully and is alive to date; however, deaths ultimately occurred in the patients with *Mucor* (patient with HCV, diabetes, and ATG induction), invasive candidiasis (previous liver transplant recipient with small bowel infarct shortly after transplant), and the candidal

Table 3: Infectious complications.

Infection	RTX $n = 55$	No RTX $n = 386$	P value
Viral, % (n)	*44 (24)*	*27 (103)*	*0.012*
CMV infection, % (n)	20 (11)	19 (72)	0.81
BK viremia, % (n)	27 (15)	13 (51)	0.011
BK nephropathy, % (n)	15 (8)	4 (14)	0.003
Other viral, % (n)	15 (8)	2 (6)	<0.001
Ebstein Barr virus, n	1	0	
Human papilloma virus, n	0	1	
Influenza A, n	0	2	
Influenza H1N1, n	1	2	
JCV-associated PML, n	1	0	
Respiratory syncytial virus, n	1	0	
Varicella zoster, n	4	1	
Number of viral infections/patient	0.6	0.3	0.005
Fungal, % (n)	*11 (6)*	*3 (10)*	*0.009*
Aspergillosis, pulmonary, n	0	4	
Candida infections, n	4	3	
Cryptococcal meningoencephalitis, n	0	3	
Nonaspergillus mould, pulmonary, n	1	0	
Mucormycosis, pulmonary, n	0	1	
Tinea corpis, disseminated, n	1	0	
Number of fungal infections/patient	0.11	0.03	0.006

Abbreviations—CMV: cytomegalovirus; JCV: JC virus; PML: progressive multifocal leukoencephalopathy.

brain abscess (62-year-old male with diabetes and ATG induction). Among RTX-treated patients, one episode of candidemia occurred, which was successfully treated, and one case of nonaspergillus mould pneumonia occurred in a previous kidney-pancreas recipient who eventually succumbed to respiratory failure. This patient had received ATG and RTX for antibody-mediated rejection one year prior.

Univariate and multivariate analyses of factors associated with the development of infection posttransplant are shown in Table 4. Recipients of deceased donor transplants and RTX-treated patients were independently associated with development of infections, with odds ratios of 2.5 and 2.2, respectively. Among the 55 RTX-treated patients, a univariate analysis of risk factors for infection was performed (not shown). No significant risk factors for infection among rituximab treated patients were identified, although several factors approached significance. Patients developing infection tended to be older (51 versus 44 yrs; $P = 0.06$), deceased donor recipients (57% versus 36% for living donors recipients; $P = 0.12$), on dialysis for a greater duration pretransplant (4.3 versus 2.2 years; $P = 0.07$), and more likely to have delayed graft function (80% versus 43% in those with immediate function $P = 0.10$).

In considering a potential immune-protective effect of IVIG, we compared the incidence of infections in RTX patients according to concomitant IVIG use. There was no difference in the rate of infection among the 26 patients receiving IVIG to those not receiving IVIG (50% versus 45%; $P = 0.72$). Additionally, there may be a concern that the patients receiving RTX for retransplantation may be at greater risk for infection due to long-standing immunosuppression. We therefore compared the incidence of infections in patients undergoing retransplant without exposure to RTX ($n = 27$) to patients receiving RTX with a primary transplant ($n = 42$). Infections occurred in 26% of the retransplanted patients without RTX versus 49% of patients receiving RTX with a primary transplant ($P = 0.06$).

4. Discussion

Over the past decade, RTX use has expanded in renal transplantation, particularly in the settings of desensitization, antibody-mediated rejection, and treatment of glomerulopathies. The safety profile of RTX in this population remains unclear, however, with conflicting data on its association with infectious complications [3, 7–14]. This study of 55 kidney transplant patients treated with RTX for its common peri- and posttransplant indications favors an association an increased risk of infections with RTX.

Through routine posttransplant BK screening and protocol biopsies, we observed a significantly greater incidence of both BK viremia and nephropathy among RTX-treated patients. Previously, Kamar et al. noted that BK virus was the most common virus detected in RTX-treated patients [8], and Habicht et al. found a nonsignificantly higher

Table 4: Risk factors for viral or fungal infection.

	% Infection	% Infection (Comparator)	Univariate *P* value	Odds ratio	Multivariate *P* value
Age ≥ 60 years	34	29 (<60 years)	0.39		
Caucasian	30	30 (non-Caucasian)	0.98		
Male gender	29	32 (female)	0.47		
Diabetes history	35	27 (no diabetes)	0.08	1.2	0.47
History chronic virus	23	31 (no virus)	0.39		
Deceased donor	38	18 (living donor)	<0.001	2.5	<0.001
Retransplant	30	30 (first transplant)	0.98		
Kidney-pancreas recipient	58	28 (kidney only)	<0.001	1.7	0.22
Perioperative ATG	32	27 (no ATG)	0.33		
Steroids at discharge	30	30 (steroid withdrawal)	0.90		
Delayed graft function	34	30 (initial function)	0.54		
Acute rejection	43	27 (no rejection)	0.007	1.5	0.12
ATG for rejection	34	30 (no ATG)	0.58		
Any ATG exposure	32	27 (no ATG exposure)	0.31		
Any RTX exposure	47	28 (no RTX exposure)	0.005	2.2	0.016

Abbreviations—ATG: antithymocyte globulin; RTX: rituximab.

rate of BK in ABO-incompatible recipients administered RTX [11]. The rates of BK viremia and nephropathy in our cohort are congruent with rates previously reported in the renal transplant population [18–21]. However, viremia and nephropathy occurred 2-3*x* more often in the RTX cohort. Similarly, an increased rate of "other" viral infections (non-CMV and non-BK related) was also noted. Varicella zoster infection occurred in 4 of 55 RTX patients compared to 1 in 386 no RTX patients. Zoster infections have been reported in other series of RTX-treated patients [11] and were even fatal in some cases [22, 23]. While none of our zoster cases suffered such fate, 3 deaths occurred among RTX patients owing to EBV-associated PTLD, RSV, and JCV-associated PML. Interestingly, we found no difference in the rate of CMV between groups. This may be due to the routine use of valganciclovir prophylaxis following acute rejection treatments.

A significantly higher incidence of fungal infections was noted in the RTX group, a similar finding albeit at a lower rate than Kamar's report (17%) [8]. In contrast to their results, however, the severity of fungal infections tended to be less in our RTX patients. All severe fungal infections, including cases of aspergillosis or cryptococcal meningitis, occurred in the no RTX group. This may have been due to the baseline characteristics of these patients, with the use of antithymocyte globulin, diabetes history, and chronic hepatitis C infection being common amongst these cases. Each case of aspergillus and cryptococcal meningitis was successfully treated.

Finally, a surprising observation in this study was the timing of infection, with a number of infections developing late (beyond 6 months) after RTX exposure. This data indicates that perhaps prophylaxis and/or close monitoring for opportunistic infections should continue for an extended period after RTX administration.

Several possible mechanisms exist for our findings. RTX may induce hypogammaglobulinemia [24, 25] which has been associated with infections in solid organ transplant populations [26]. While IgG monitoring was not routinely performed in our cohorts it is plausible that depletion of BK or other viral-specific IgG, may have occurred. Previous data demonstrated that low BK virus IgG levels correlated with a higher degree of BK replication [27]. BK and other non-CMV viral infections seen in our cohort either lacked prophylactic strategies (i.e., JC virus, RSV) or occurred late (>6 months) after RTX exposure, making prevention and/or monitoring for these infections difficult. RTX may have long-term effects on B-cell depletion, especially in the setting of renal dysfunction [16, 17]. This may account for some of the late onset infections seen in our cohort. Furthermore, as B-cells are known antigen-presenting cells, depletion of B-cells may hinder virus-specific T-cell responses and immune responses to fungal pathogens.

The role of concomitant immunosuppressive therapies should be appreciated. While we observed no differences in maintenance immunosuppressive drug levels or dosages, we did observe a higher cumulative amount of ATG given to the RTX-treated patients. To eliminate the influence of augmented immunosuppression with rejection therapies, we evaluated the incidence of viral and fungal infections in patients without any rejections. The results were similar to the cohort as a whole, suggesting that even when used without additional augmented immunosuppression, RTX may still promote the development of infections.

This study has several limitations, most of which relate to its retrospective nature. Without the use of a randomized, prospective design, it is difficult to clearly ascertain the risk of

one antibody agent over another. As mentioned previously, IgG levels were not checked, and therefore the contribution of hypogammaglobulinemia could not be assessed. In our population, we did not observe a "protective effect" of IVIG, perhaps owing to the prolonged hypogammaglobulinemic effects observed with RTX [24, 25]. Finally, our sample size was not large enough to determine statistically significant risks for infection among the RTX-treated cohort, although trends were seen in those who were older, on dialysis longer, deceased donor transplants, and those with DGF.

In conclusion, we found a significantly higher rate of viral and fungal infections in patients treated with RTX. Most infections observed were those for which established prophylactic strategies do not exist, and some may occur late after rituximab exposure. Close monitoring for infections and expanded use of prophylactic strategies should be considered in patients receiving RTX.

Abbreviations

AMR: Antibody mediated rejection
ATG: Antithymocyte globulin
CMV: Cytomegalovirus
DSA: Donor specific antibodies
HLA: Human leukocyte antigen
IL2ra: Interleukin-2 receptor antagonist
IVIG: Intravenous immunoglobulin
PRA: Panel reactive antibody
RTX: Rituximab.

Conflicts of Interests

The authors declare no conflict of interests.

Acknowledgments

The authors would like to thank the organ transplant coordinators and clinical research coordinators at the Houston Methodist J. C. Walter Jr Transplant Center in Houston, TX, USA for their maintenance of transplant center data and assistance in attaining clinical information.

References

[1] M. D. Pescovitz, "Rituximab, an anti-CD20 monoclonal antibody: history and mechanism of action," *The American Journal of Transplantation*, vol. 6, no. 5, part 1, pp. 859–866, 2006.

[2] Y. T. Becker, M. Samaniego-Picota, and H. W. Sollinger, "The emerging role of rituximab in organ transplantation," *Transplant International*, vol. 19, no. 8, pp. 621–628, 2006.

[3] A. A. Vo, M. Lukovsky, M. Toyoda et al., "Rituximab and intravenous immune globulin for desensitization during renal transplantation," *The New England Journal of Medicine*, vol. 359, no. 3, pp. 242–251, 2008.

[4] H. Genberg, G. Kumlien, L. Wennberg, U. Berg, and G. Tydén, "ABO-incompatible kidney transplantation using antigen-specific immunoadsorption and rituximab: a 3-year follow-up," *Transplantation*, vol. 85, no. 12, pp. 1745–1754, 2008.

[5] G. L. Bumgardner, I. Hardie, R. W. G. Johnson et al., "Results of 3-year phase III clinical trials with daclizumab prophylaxis for prevention of acute rejection after renal transplantation," *Transplantation*, vol. 72, no. 5, pp. 839–845, 2001.

[6] B. Nashan, R. Moore, P. Amlot, A.-G. Schmidt, K. Abeywickrama, and J.-P. Soulillou, "Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients," *The Lancet*, vol. 350, no. 9086, pp. 1193–1198, 1997.

[7] S. A. Grim, T. Pham, J. Thielke et al., "Infectious complications associated with the use of rituximab for ABO-incompatible and positive cross-match renal transplant recipients," *Clinical Transplantation*, vol. 21, no. 5, pp. 628–632, 2007.

[8] N. Kamar, O. Milioto, B. Puissant-Lubrano et al., "Incidence and predictive factors for infectious disease after rituximab therapy in kidney-transplant patients," *The American Journal of Transplantation*, vol. 10, no. 1, pp. 89–98, 2010.

[9] A. S. Munoz, A. A. Rioveros, C. B. Cabanayan-Casasola, R. A. Danguilan, and E. T. Ona, "Rituximab in highly sensitized kidney transplant recipients," *Transplantation Proceedings*, vol. 40, no. 7, pp. 2218–2221, 2008.

[10] Z. Kaposztas, H. Podder, S. Mauiyyedi et al., "Impact of rituximab therapy for treatment of acute humoral rejection," *Clinical Transplantation*, vol. 23, no. 1, pp. 63–73, 2009.

[11] A. Habicht, V. Bröker, C. Blume et al., "Increase of infectious complications in ABO-incompatible kidney transplant recipients-a single centre experience," *Nephrology Dialysis Transplantation*, vol. 26, no. 12, pp. 4124–4131, 2011.

[12] C. H. Baek, W. S. Yang, K. S. Park, D. J. Han, J. B. Park, and S. K. Park, "Infectious risks and optimal strength of maintenance immunosuppressants in rituximab-treated kidney transplantation," *Nephron Extra*, vol. 2, no. 1, pp. 66–75, 2012.

[13] G. Tydén, H. Genberg, J. Tollemar et al., "A randomized, doubleblind, placebo-controlled, study of single-dose rituximab as induction in renal transplantation," *Transplantation*, vol. 87, no. 9, pp. 1325–1329, 2009.

[14] J. Kahwaji, A. Sinha, M. Toyoda et al., "Infectious complications in kidney-transplant recipients desensitized with rituximab and intravenous immunoglobulin," *Clinical Journal of the American Society of Nephrology*, vol. 6, no. 12, pp. 2894–2900, 2011.

[15] Thymoglobulin (Anti-thymocyte globulin rabbit), *Package Insert*, Genzyme, Cambridge, Mass, USA.

[16] H. Genberg, A. Hansson, A. Wernerson, L. Wennberg, and G. Tydén, "Pharmacodynamics of rituximab in kidney transplantation," *Transplantation*, vol. 84, supplement 12, pp. S33–S36, 2007.

[17] C. A. Vieira, A. Agarwal, B. K. Book et al., "Rituximab for reduction of anti-HLA antibodies in patients awaiting renal transplantation: 1. Safety, pharmacodynamics, and pharmacokinetics1," *Transplantation*, vol. 77, no. 4, pp. 542–548, 2004.

[18] I. A. Memon, B. A. Parikh, M. Gaudreault-Keener, R. Skelton, G. A. Storch, and D. C. Brennan, "Progression from sustained BK viruria to sustained BK viremia with immunosuppression reduction is not associated with changes in the noncoding control region of the BK virus genome," *Transplantation*, vol. 2012, Article ID 761283, 7 pages, 2012.

[19] H. H. Hirsch, D. C. Brennan, C. B. Drachenberg et al., "Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations," *Transplantation*, vol. 79, no. 10, pp. 1277–1286, 2005.

[20] D. C. Brennan, I. Agha, and D. L. Bohl, "Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive

immunosuppression reduction," *The American Journal of Transplantation*, vol. 5, no. 3, pp. 582–594, 2005.

[21] E. Ramos, C. B. Drachenberg, R. Wali, and H. H. Hirsch, "The decade of polyomavirus BK-associated nephropathy: state of affairs," *Transplantation*, vol. 87, no. 5, pp. 621–630, 2009.

[22] A. Bermúdez, F. Marco, E. Conde, E. Mazo, M. Recio, and A. Zubizarreta, "Fatal visceral varicella-zoster infection following rituximab and chemotherapy treatment in a patient with follicular lymphoma," *Haematologica*, vol. 85, no. 8, pp. 894–895, 2000.

[23] L. M. Mcilwaine, E. J. Fitzsimons, and R. L. Soutar, "Inappropriate antidiuretic hormone secretion, abdominal pain and disseminated varicella-zoster virus infection: an unusual and fatal triad in a patient 13 months post Rituximab and autologous stem cell transplantation," *Clinical and Laboratory Haematology*, vol. 23, no. 4, pp. 253–254, 2001.

[24] E. Irie, Y. Shirota, C. Suzuki et al., "Severe hypogammaglobulinemia persisting for 6 years after treatment with rituximab combined chemotherapy due to arrest of B lymphocyte differentiation together with alteration of T lymphocyte homeostasis," *International Journal of Hematology*, vol. 91, no. 3, pp. 501–508, 2010.

[25] N. Cooper, E. G. Davies, and A. J. Thrasher, "Repeated courses of rituximab for autoimmune cytopenias may precipitate profound hypogammaglobulinaemia requiring replacement intravenous immunoglobulin," *British Journal of Haematology*, vol. 146, no. 1, pp. 120–122, 2009.

[26] S. Mawhorter and M. H. Yamani, "Hypogammaglobulinemia and infection risk in solid organ transplant recipients," *Current Opinion in Organ Transplantation*, vol. 13, no. 6, pp. 581–585, 2008.

[27] S. Hariharan, E. P. Cohen, B. Vasudev et al., "BK virus-specific antibodies and BKV DNA in renal transplant recipients with BKV nephritis," *The American Journal of Transplantation*, vol. 5, no. 11, pp. 2719–2724, 2005.