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Treatment of Chronic Active Antibody-mediated Rejection With Pulse Steroids, IVIG, With or Without Rituximab is Associated With Increased Risk of Pneumonia

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Background. The risk of infection associated with specific treatments of chronic active antibody-mediated rejection (cAMR) after kidney transplantation remains unknown. **Methods.** This was a single-center study of kidney transplant recipients treated with pulse steroids, intravenous immunoglobulin (IVIG) ± rituximab for biopsy-confirmed cAMR. The control group consisted of age- and race-matched patients who underwent donor-specific antibody-based protocol biopsies but had no rejection. We collected data on BK virus (BKV), cytomegalovirus (CMV), urinary tract infection (UTI), and pneumonia postbiopsy. **Results.** There were 49 patients in each group. In those with cAMR, 21 (43%) were treated with steroids, IVIG, and rituximab; the remaining received steroids and IVIG only. The risk of graft failure was greater in the cAMR group [22 (45%) vs. 3 (6%), $P < 0.001$]. Kaplan-Meier analyses demonstrated a significantly greater risk of pneumonia in the cAMR group ($P = 0.02$). This was confirmed by multivariable Cox regression analyses [Hazard ratio (HR) = 6.04, $P = 0.027$, 95% CI, 1.22-29.75]. None of the patients with pneumonia were affected by opportunistic pathogens. Additionally, the risk of CMV, UTI, and BKV was not increased. Rituximab was not independently associated with any of the infections studied. **Conclusions.** Treatment of cAMR, but not rituximab, was associated with a 6-fold increased risk of pneumonia. Additional studies are needed to determine the safety and efficacy of prolonged antimicrobial prophylaxis and monitoring strategies, including for hypogammaglobulinemia, to reduce the risk of pneumonia following the treatment of cAMR.

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INTRODUCTION

Chronic active antibody-mediated rejection (cAMR) is a leading cause of kidney allograft failure, despite overall

advancements in the treatment of acute rejection.[1] There is currently no FDA-approved treatment for cAMR although therapeutic strategies include pulse steroids, intravenous immunoglobulin (IVIG), plasma exchange (PLEX), rituximab, and less commonly, antithymocyte globulin or bortezomib.[2,3] Several studies have demonstrated that treatment of cAMR may reduce the risk of graft loss or mitigate the loss of eGFR short term.[4-8] However, conflicting studies question treatment efficacy and raise concern regarding complications of over-immunosuppression, namely infection.[3,9-13] Therefore, in the era of standardized antirejection and prophylactic antimicrobial treatment protocols, the infection risk after cAMR treatment remains unknown.

A study of 65 patients with cAMR suggested that treatment was associated with an increased rate of BK virus (BKV), cytomegalovirus (CMV), and bacterial infections, although these differences were not statistically significant.[5] Another study of 62 patients with cAMR demonstrated an increased risk of infection and hospitalization for those who received treatment with rituximab, IVIG, and PLEX, although only 23 patients had received treatment.[13] Notably, infectious complications were not the primary outcome of either of these studies.

Our aim was to determine the specific rates of common infections after transplant, namely BKV, CMV, urinary tract infection (UTI), and pneumonia, following cAMR therapy

with pulse steroids, IVIG ± rituximab, with standard antimicrobial prophylaxis for 3 months post-treatment. Our observation may provide clarification on infectious complications and mitigation strategies for cAMR.

MATERIALS AND METHODS

Patients

This was a single-center, prospective study of kidney transplant recipients who underwent biopsy between January 1, 2013, and December 31, 2016. We included patients who were diagnosed with biopsy-proven cAMR based on BANFF criteria and treated with pulse steroids, IVIG ± rituximab (cAMR group).[14,15] All patients in this group had human leukocyte antigen (HLA) donor-specific antibodies (DSA). The second group of age- and race-matched patients who underwent DSA-based protocol biopsy in the same-time interval and had no rejection was designated as the control group. Patients were followed for 2 years from the index biopsy, or until graft failure or patient death, whichever occurred first.

Study Protocol and Data Collection

This study was approved by the University of Wisconsin School of Medicine and Public Health Institutional Review Board. Data collection included basic demographic information, date of kidney transplantation, age, race, gender, induction immunosuppression, cause of the end-stage renal disease (ESRD), and type of transplant. A history of rejection before the index biopsy as well as the type of rejection was recorded. We also collected information regarding the history of infection (BKV, CMV, UTI, or pneumonia) at any time preceding the index biopsy; among those with a history of infection, the type of infection that most immediately preceded the index biopsy was recorded. We collected the indication for biopsy, serum creatinine (Scr), eGFR and urine protein to creatinine ratio (UPC), histopathology of kidney biopsy, DSA information, treatment received for cAMR, and immunosuppression doses 2–6 weeks post index biopsy in both groups.

DSA was recorded as the sum of mean fluorescence intensity (MFI) for classes I and II as described previously; immunodominant DSA was defined as the DSA with maximum MFI and presented as MFI_{max}.[16,17] A value of 0 was assigned for UPC when urine protein was undetectable.

For infectious complications after treatment for cAMR (or biopsy in the case of the control group), we collected data on four types of infections: (1) BKV viremia by polymerase chain reaction (PCR) and/or BKV nephropathy diagnosed based on biopsy with tubulitis and SV-40 viral inclusions, (2) CMV viremia by PCR and/or evidence of tissue-invasive CMV disease diagnosed clinically or by biopsy, (3) pneumonia, which required radiologic findings consistent with pneumonia, along with clinical symptoms and/or positive sputum culture, and (4) UTI as defined by clinical symptoms and positive urine culture. We also recorded information regarding graft failure, patient death, and graft function at 2 years after index biopsy. Graft failure was defined as a return to dialysis, retransplant, or patient death. Last follow-up was censored at patient death or graft failure for those who experienced it, or at 2 years (±1 month) after biopsy for those with a functioning graft.

Induction and Maintenance Immunosuppression

Patients undergoing kidney transplant received induction immunosuppression with a depleting agent (antithymocyte globulin, alemtuzumab, or OKT3) or nondepleting agent (basiliximab) based on immunological risk factors as described previously.[17] Patients were typically maintained on a triple immunosuppressive regimen with a calcineurin inhibitor (tacrolimus), antiproliferative agent (mycophenolate mofetil or mycophenolic acid), and steroids. Some patients underwent early steroid withdrawal based on clinical protocol and/or patient request. Medication doses and drug levels were adjusted individually at physician discretion based on the patient's clinical condition, including infection, malignancy, and rejection.

Biopsy Indication

A majority of kidney allograft biopsies at our institution are done for-cause, mainly due to an unexplained rise in serum creatinine or proteinuria. We also perform protocol biopsies at 3- and 12-months post-transplant among patients with pretransplant DSA. Post-transplant DSA is monitored closely as previously described, and patients who develop de novo DSA undergo protocol biopsy irrespective of graft function.[16] All patients treated for cAMR undergo a follow-up biopsy between 6 and 12 weeks after treatment.

Treatment of cAMR

Patients underwent treatment for cAMR based on our protocol for patients with late rejection (>3 months post-transplant) with patients receiving a steroid pulse (starting with a 50–100 mg bolus of intravenous dexamethasone followed by an oral prednisone taper) and 500 mg/kg of IVIG every 2 weeks for 3 doses. Some patients also received a single dose of 375 mg/m^2 of rituximab, based on clinical and immunophenotypic features as previously described.[8]

Monitoring and Antimicrobial Prophylaxis

Quantitative serum BKV PCR is monitored per protocol every 2 weeks for the first 3 months post-transplant, then monthly until 12 months post-transplant, and at the time of for-cause kidney biopsy as described before.[18] Immunosuppression is decreased for plasma BKV PCR >1000 copies/ml. Use of valganciclovir for CMV prophylaxis or acyclovir for herpes virus prophylaxis is based on the induction immunosuppression used and risk for infections.[18] Similar monitoring and prophylaxis strategies are employed with the treatment of cAMR. Specifically, patients are started on a 3-month course of prophylactic trimethoprim/sulfamethoxazole for *Pneumocystis jiroveci* pneumonia, acyclovir or valganciclovir for CMV, and clotrimazole troches for fungal infections.

Statistical Analysis

Continuous data were compared using Student's *t*-test or the Wilcoxon rank sum test, as appropriate, while categorical data were analyzed using chi-square test or Fisher exact test. *P* values ≤0.05 were considered statistically significant. Risk factors associated with infection were studied using Kaplan-Meier analyses and multivariate models were constructed using relevant clinical variables. Two models were constructed to assess the risk of infections based on the different treatment regimens of cAMR (with and without rituximab).

RESULTS

Baseline Characteristics

Baseline characteristics are included in Table 1. There were 49 patients in both cAMR and control groups (98

TABLE 1.
Baseline characteristics

Variables	cAMR (n = 49)	Control (n = 49)	P
Male n, (%)	31 (63%)	30 (61%)	0.83
Mean age transplant (years)	45.0 ± 11.6	45.3 ± 11.6	0.87
Caucasian n, (%)	44 (90%)	44 (90%)	
Causes of ESRD n, (%)			0.08
Glomerulonephritis	19 (39%)	10 (20%)	
Diabetes	9 (18%)	8 (17%)	
Hypertension	4 (8%)	5 (10%)	
PKD	9 (18%)	10 (20%)	
Other	8 (17%)	16 (33%)	
Mean number of transplants	1.3 ± 0.6	1.4 ± 0.7	0.27
Mean HLA mismatch (of 6)	4.2 ± 1.1	4.2 ± 1.3	0.80
Living donor transplant n, (%)	20 (41%)	22 (45%)	0.68
Induction therapy n, (%)			0.19
IL-2 receptor antibodies	29 (60%)	20 (41%)	
Antithymocyte globulin	9 (18%)	21 (43%)	
Alemtuzumab	6 (12%)	5 (10%)	
OKT3	1 (2%)	0	
Other/unknown	4 (8%)	3 (6%)	

ESRD, end-stage renal disease.

patients total). Patients were matched for age and race by design, and the remaining baseline characteristics including gender, cause of ESRD, mean number of transplants, mean number of HLA mismatches, donor type (living versus deceased), and induction therapy were not different between the 2 groups.

History of Prior Rejection and Infection

There was no difference in the number of patients with a history of one of the 4 infection types studied among those with cAMR versus the control group (53% versus 43%), or in the mean number of prior infections (Table 2). Among those with infections, there was no difference in the type of infection that most closely preceded the index biopsy. However, there was a difference in prior episodes of rejection, with 47% of

TABLE 2.
History of infection and rejection before index biopsy

	cAMR (n = 49)	Control (n = 49)	P
Number of patients with infection before index biopsy n, (%)	26 (53%)	21 (43%)	0.31
Mean number of prior infections	1.32 ± 1.98	0.77 ± 1.46	0.12
Type of infection preceding index biopsy, (%)			0.93
BKV	4 (8%)	7 (15%)	
CMV	2 (4%)	1 (2%)	
UTI	14 (29%)	5 (10%)	
Pneumonia	6 (12%)	7 (15%)	
Number of patients with rejection before index biopsy n, (%)	23 (47%)	4 (8%)	<0.001
Mean number of prior rejection episodes	0.69 ± 0.89	0.08 ± 0.28	<0.001
Type of prior rejection			0.45
AMR/mixed	16 (32%)	2 (4%)	
TCMR	7 (15%)	2 (4%)	

AMR, antibody-mediated rejection; BKV, BK virus; CMV, cytomegalovirus; TCMR, T-cell-mediated rejection; UTI, urinary tract infection.

patients with cAMR having a prior episode of rejection compared with 8% of patients in the control group.

Renal Function and Immunopathology at the Time of Biopsy

Mean time from transplant to biopsy was 110.9 ± 62.9 months in the cAMR group versus 44.1 ± 71.0 months in the control group. Data at the time of biopsy are demonstrated in Table 3. As expected, patients with cAMR had higher serum creatinine, lower eGFR and higher UPC than those without cAMR. Similarly, patients with cAMR had a higher class II sum MFI as well as higher immunodominant MFI. Biopsy findings in patients with cAMR were consistent with the BANFF diagnosis, with evidence of microvascular inflammation (MVI), as well as transplant glomerulopathy (cg), and higher chronicity score (ci+ct+cg+cv), compared with those in the control group.

Patient and Allograft Outcomes

Mean follow-up was 19.4 ± 7.1 months for the cAMR group versus 23.5 ± 2.5 months for the control group (Table 4). Of the patients treated for cAMR, 21 (43%) were treated with pulse steroids, IVIG and rituximab, whereas 28 (57%) were treated with steroids and IVIG only. Maintenance immunosuppression was similar after 2–6 weeks after index biopsy in the cAMR and control groups, except for the mean prednisone dose, which was higher in those with cAMR, as would be expected given the treatment with pulse steroids. A total of 22 (45%) grafts failed within 2 years of diagnosis of cAMR compared with 3 (6%) in the control group ($P < 0.001$). After censoring for death, 16 (33%) patients in the cAMR group experienced graft loss compared with 1 (2%) in the control group ($P < 0.001$). In surviving patients, kidney function was worse in the cAMR group at 2 years.

Infections After Treatment for cAMR

In the cAMR group, 3 (6%) patients experienced BKV, 2 (4%) had CMV, 3 (6%) had UTIs and 8 (16%) had pneumonia, compared with 9 (18%), 2 (4%), 11 (22%), and 2 (4%), respectively, in the control group (Figure 1 and Table 5). Figure 1 displays the Kaplan-Meier survival curves for each of the 4 infection types studied. In the 2 years after treatment for cAMR, there was a significantly greater incidence of pneumonia compared with the control group. There was no significant difference in the incidence of the other 3 infections.

Among those diagnosed with pneumonia in the cAMR group, 6 were diagnosed with community-acquired pneumonia (CAP) pneumonia based on radiologic imaging and clinical symptoms; 3 of these patients underwent bronchoscopy and bronchoalveolar lavage, but no cultures returned positive. The remaining 2 patients were diagnosed with aspiration pneumonia again based on radiologic imaging and clinical symptoms. The 2 patients with pneumonia in the control group were diagnosed with CAP based on imaging and clinical symptoms. Among those with pneumonia, there were no opportunistic pathogens identified, and no patients had concomitant respiratory viral infections.

As demonstrated in Table 5, patients treated for cAMR had a significantly greater risk of pneumonia (HR 6.04; $P = 0.027$; 97% CI, 1.22-29.75), without increased risk for BKV, CMV, or UTI. Use of rituximab did not confer additional risk for any of the 4 infections studied. Male gender was associated with reduced risk of UTI (HR 0.03; $P = 0.002$; 97% CI, 0.005-0.29).

TABLE 3.

Kidney function and immunopathology at time of biopsy

	Variables	cAMR (n = 49)	Control (n = 49)	P
DSA	Class I MFI$_{sum}$	3917 ± 5718 (n = 24)	2486 ± 4545 (n = 22)	0.36
	Class II MFI$_{sum}$	19,890 ± 22,445 (n = 40)	4509 ± 5303 (n = 37)	<0.001
	Immunodominant MFI$_{max}$	11,159 ± 9,298	3954 ± 5469	<0.001
Kidney function	Scr (mg/dl)	2.2 ± 1.6	1.4 ± 0.5	<0.001
	eGFR (ml/min)	38.9 ± 17.8	56.4 ± 20.0	<0.001
	UPC (g/g)	1.6 ± 1.8	0.2 ± 0.2	<0.001
Pathology	i score (0–3)	0.26 ± 0.63	0.02 ± 0.14	0.01
	t score (0–3)	0	0	
	v score (0–3)	0.02 ± 0.14	0	
	MVI ptc + g (0–6)	2.90 ± 1.01	0	
	ptc (0–3)	1.20 ± 0.68	0	
	g (0–3)	1.61 ± 0.84	0	
	C4d (0–3)	1.42 ± 1.37	0	
	cg (0–3)	1.98 ± 0.95	0.04 ± 0.20	<0.001
	ci+ct+cg+cv (0–12)	5.73 ± 2.30	2.0 ± 2.14	<0.001

DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; MFI, mean fluorescence intensity; MVI, microvascular inflammation; UPC, urine protein to creatinine ratio.

DISCUSSION

Our study suggests that kidney transplant recipients who undergo therapy with pulse steroids, IVIG ± rituximab for cAMR are at increased risk of developing pneumonia within 2 years after treatment, with a hazard ratio of 6.04. There was no difference in the incidence of CMV, BKV, or UTI between the two groups. However, male gender was associated with a reduced risk of UTI.

For patients diagnosed with cAMR, the ideal treatment remains uncertain, and there are likely multiple pathologic processes that require interruption to slow the rate of decline in renal function and graft loss. However, the increase in immunosuppression for patients treated for cAMR may be complicated by increased side effects such as infection. Therefore, the benefits of potentially prolonging graft survival must be weighed against increased morbidity and mortality of increased immunosuppression. However, it has been difficult to accurately estimate these risks due to lack of data regarding complications such as infection.

Recent consensus guidelines for the treatment of cAMR recommend the use of PLEX, IVIG, and steroids for treatment, with the possible addition of rituximab in the setting of de novo DSA, despite lack of evidence of efficacy.[3] They do state that treatment needs to be weighed against the consequences of infection and cost. In our study, we sought to better elucidate the risk of infectious complications after treatment of cAMR with IVIG and steroids with or without rituximab. Our results indicate that patients treated for cAMR had a significantly higher risk of pneumonia (HR of 6.04) in the subsequent 2 years of follow-up than our control group. We included aspiration pneumonia in our primary outcomes because in theory all infectious complications may be related directly or indirectly to the overall immune status of the transplant recipient. Notably, none of the patients with pneumonia were affected by opportunistic pathogens. We did not observe an increased risk of UTI, BKV, or CMV infection. Similarly, treatment with rituximab for cAMR was not independently associated with risk of any infections. It is possible that the standard of care antimicrobial prophylaxis and monitoring strategies were sufficient in preventing these infections, but not pneumonia. Future measures to assess and reduce the risk of pneumonia after cAMR treatment could involve serum IgG assessments and IVIG therapy for hypogammaglobulinemia, although the efficacy of this would need to be ascertained.
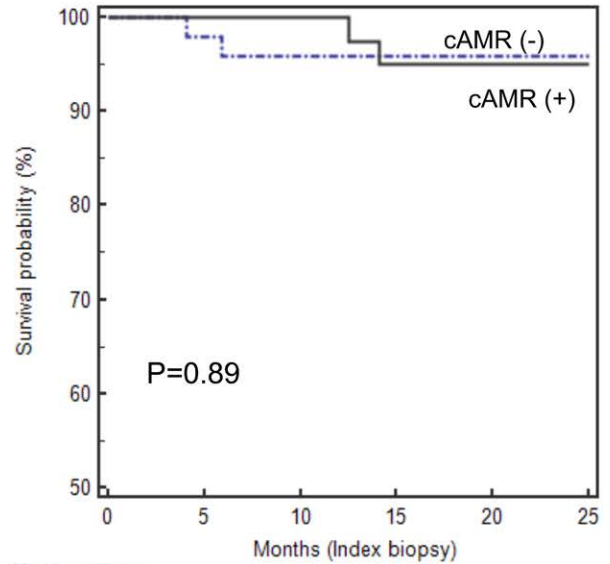
Much of the challenge in accurately determining infectious risks has been the small sample size in studies, low frequency of infectious complications, and variability in the agents used

TABLE 4.

Treatment and outcomes at 2 years post index biopsy

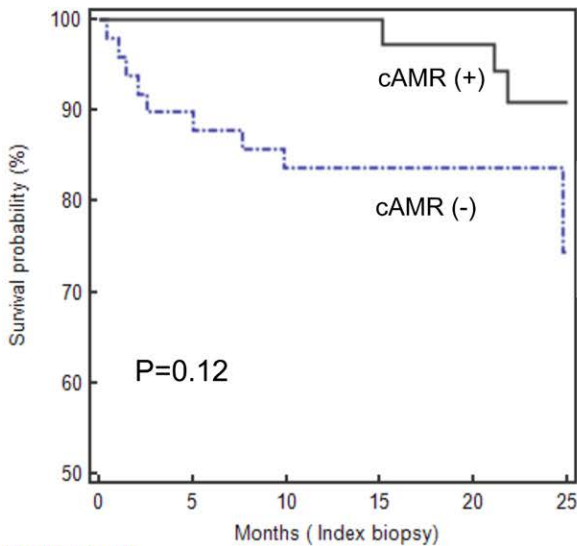|	Variables	cAMR (n = 49)	Control (n = 49)	P
Treatment for cAMR	Pulse steroid + IVIG, n (%)	28 (57%)	0	
	Pulse steroid + IVIG + rituximab n (%)	21 (43%)	0	
Maintenance immunosuppression 2–6 wk post-biopsy	Mean tacrolimus level (ng/mL)	6.56 ± 1.89	6.83 ± 1.72	0.50
	Mean mycophenolic acid dose (mg)	1297 ± 273	1236 ± 333	0.35
	Mean prednisone dose (mg)	12.3 ± 7.1	6.9 ± 2.25	<0.001
Kidney function at 2 y	eGFR (ml/min/1.73m^2)	40.8 ± 14.3	51.7 ± 18.0	0.03
	SCr (mg/dl)	1.74 ± 0.69 (n = 20)	1.31 ± 0.55 (n = 42)	0.12
Outcome after 2 y	Total number of graft failure, n (%)	22 (45%)	3 (6%)	<0.001
	Death-censored graft failure, n (%)	16 (33%)	1 (2%)	<0.001

cAMR, chronic active antibody-mediated rejection; eGFR, estimated glomerular filtration rate; IVIG, intravenous immunoglobulin.

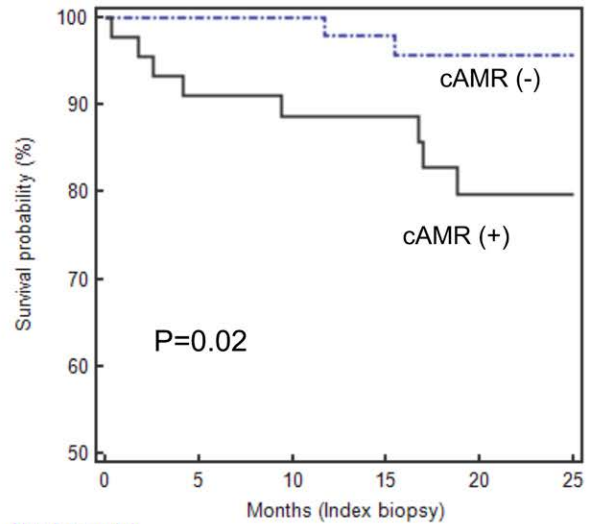**FIGURE 1.** Infectious complications after treatment for cAMR vs control. AMR, antibody-mediated rejection; BKV, BK virus; cAMR, chronic active antibody-mediated rejection; CMV, cytomegalovirus; UTI, urinary tract infection.

to treat cAMR, with various studies providing discrepant results. A single-center study by Chiu et al. examined the risk of infection and mortality among those with cAMR treated with plasmapheresis and at least one other agent; while there was no statistical difference in major complications (infection, leukopenia, or mortality), the number of adverse events per patient was greater than in the group who received supportive treatment.[4] However, a randomized, double-blinded, placebo-controlled trial of IVIG plus rituximab did not demonstrate any increased risk of adverse events, and there were no opportunistic infections over a year of follow-up.[12]

Our study findings are limited by small sample size and the inherent difficulties of an observational study, although this is the largest dedicated study examining the effect of various treatments for cAMR on infectious risk. The selection of a control group was also a challenge. We selected an age- and race-matched group of patients that had undergone a biopsy for DSA but had no rejection. The ideal control group

TABLE 5.

Factors associated with infectious complications after treatment of cAMR

	Variables	HR	P	95% CI of HR
Risk factors for BKV infection (multivariable analyses)				
Model 1	Male	0.88	0.84	0.28-2.82
	Depletion induction	1.07	0.90	0.34-3.37
	Rituximab Rx for cAMR	0.33	0.30	0.04-2.63
Model 2	Male	0.91	0.87	0.28-2.88
	Depletion induction	0.97	0.96	0.31-3.09
	Treatment of cAMR	0.37	0.14	0.09-1.40
Risk factors for CMV infection (multivariable analyses)				
Model 1	Male	0.56	0.56	0.08-3.97
	Depletion induction	0.39	0.42	0.04-3.81
	Rituximab Rx for cAMR	1.13	0.92	0.11-11.08
Model 2	Male	0.56	0.56	0.07-4.0
	Depletion induction	0.38	0.41	0.04-3.85
	Treatment of cAMR	0.97	0.98	0.13-7.21
Risk factors for UTI (multivariable analyses)				
Model 1	Male	0.03	0.002	0.005-0.29
	Depletion induction	1.25	0.68	0.43-3.62
	Rituximab Rx for cAMR	1.41	0.59	0.39-5.09
Model 2	Male	0.04	0.001	0.005-0.30
	Depletion induction	1.08	0.88	0.37-3.14
	Treatment of cAMR	0.32	0.08	0.09-1.17
Risk factors for pneumonia (multivariable analyses)				
Model 1	Male	0.35	0.11	0.10-1.26
	Depletion induction	0.87	0.83	0.24-3.14
	Rituximab Rx for cAMR	1.60	0.50	0.41-6.32
Model 2	Male	0.31	0.07	0.09-1.12
	Depletion induction	1.23	0.75	0.33-4.56
	Treatment of cAMR	6.04	0.027	1.22-29.75

BKV, BK virus; cAMR, chronic active antibodymediated rejection; CI, confidence interval; CMV, cytomegalovirus; HR, hazard ratio; UTI, urinary tract infection.

would have been patients with cAMR who were not treated. However, untreated patients with cAMR have poor outcomes at our institution.[6] As a result, nearly all patients with cAMR undergo therapy as outlined in this paper. Finally, lead-time to index biopsy was longer in the treatment group, which was exposed to higher overall immunosuppression. Notably; however, the patients with cAMR did not have a higher rate of prior infectious complications.

In summary, treatment of cAMR, but not rituximab, was associated with a 6-fold increased risk of pneumonia. Additional studies are needed to determine the safety and efficacy of prolonged antimicrobial prophylaxis and monitoring strategies including for hypogammaglobulinemia, to reduce the risk of pneumonia following the treatment of cAMR.

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