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# Infectious Complications of Induction Therapies in Kidney Transplantation

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**Background:** *Cytomegalovirus* (CMV) and BK virus (BKV) are post-transplant opportunistic viral infections that affect patient and graft survival. This study was designed to evaluate the risk of BKV nephropathy and CMV disease in kidney transplant recipients who received induction therapy with ATG or basiliximab.

**Material/Methods:** We retrospectively analyzed information on 257 adult patients who underwent kidney transplantation between January 2007 and 2017. Patients were categorized into 3 groups according to the induction therapies. The primary endpoint was the onset of CMV disease or biopsy-confirmed BKV nephropathy. The secondary endpoints were biopsy-proven rejection episodes, graft loss, loss to follow-up, and death.

**Results:** We followed 257 patients for a median of 55.5 months. The incidence of CMV disease was significantly higher in the only ATG group compared to the group without induction treatment ($p<0.001$). There was no significant difference in the incidence of BKV nephropathy among groups ($p>0.05$). The dosage of ATG (OR, 10.685; 95% CI, 1.343 5 to 85.009; P=0.025) was independent risk factor for death.

**Conclusions:** This study demonstrated that a higher dosage of ATG in high-risk patients is associated with an increased risk of CMV disease and patient death, also, reducing the dosage may be a rational strategy for increasing graft and patient's survival.

**MeSH Keywords:** **BK Virus • Cytomegalovirus • Kidney Transplantation**

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## Background

Kidney transplantation is the best treatment for the end-stage renal disease, but rejection episodes and adverse effects of immunosuppressive agents remain major complications. Anti-lymphocyte therapies are widely used for the prevention and treatment of rejection [1,2]. Extended use of induction therapies and intensification of maintenance immunosuppression increase infection rates. The dosing strategy of anti-lymphocyte therapies plays a major role in T cell depletion and infection risk [2]. Anti-thymocyte globulin (ATG) and basiliximab are the most frequently used induction therapies [3]. ATG is a lymphocyte-depleting polyclonal antibody that targets multiple immunological epitopes. There are several ATG preparations, which differ from regard to the source of human T cells and the inoculated animals [3,4]. Basiliximab is a monoclonal antibody that targets the interleukin-2 receptor [1–4].

*Cytomegalovirus* (CMV) infection is the most common viral disease in transplant patients; it negatively affects graft and patient survival. Nearly one-quarter of kidney transplant recipients have CMV disease, mostly after the first 3 months of transplantation [2,5]. The risk factors of CMV disease are serostatus of the donor and recipient, previous rejection episodes, and intense immunosuppression [2,6].

BK virus is a common post-transplant opportunistic viral infection that affects nearly 15% of renal transplant recipients [8,9]. Over-immunosuppression, male sex, older recipient age, prior rejection episodes, number of HLA mismatches, prolonged cold ischemia time, and ureteral stent placement are the risk factors for BKV nephropathy. Studies describing the association between BKV nephropathy, CMV infection, and ATG usage have many limitations, including the following: (1) ATG inhibits CMV-specific immune reconstitution and increases the risk of CMV disease [6,7], but this adverse effect does not determine exactly when CMV prophylaxis is administered; (2) Evidence of the relationships among BKV nephropathy, CMV infection, and ATG usage is limited and controversial [8,9], and while some studies showed that ATG usage is a risk factor for BKV nephropathy, others reported that cumulative immunosuppression is more important than the specific drug [2,8,9]; and (3) doses of ATG are usually low (1–1.5 mg/kg), the duration in previous studies has been short (5–7 days), and the appropriate dose for preventing the development of BKV nephropathy and CMV infection in high-risk patients has not been defined. The present study was designed to evaluate the risk of BKV nephropathy and CMV disease in kidney transplant recipients who received induction therapy with ATG or basiliximab.

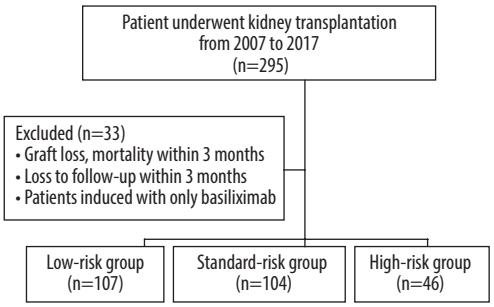


**Figure 1.** Flow chart of patient disposition.

## Material and Methods

### Study design and population

We performed a retrospective cohort study of adult (≥18 years old) patients who received first kidney transplantation without multiple organ transplantation from 1 January 2007 to 1 January 2017 at our center. The patient's data was obtained from the hospital database. A total of 295 participants were initially included. The following exclusion criteria were applied: (1) graft loss or mortality within 3 months after transplant (n=8); (2) loss to follow-up within 3 months after transplant (n=15); and (3) patients induced with only basiliximab (n=15). The remaining 257 participants were followed from 3 months after transplant until death or 31 December 2018. Patients were divided into 3 categories according to induction therapy: no induction, induction with only ATG, and induction with basiliximab and ATG (Figure 1).

### Immunosuppression

For the purpose of this analysis, patients were categorized into 3 groups; (1) Low-risk patients (living donor with panel-reactive antibody <%20), (2) Standard-risk patients (living donor with panel-reactive antibody >20%, the deceased donor with panel-reactive antibody <20%), and (3) High-risk patients (the deceased donor with PRA>%20 or positive B flow cytometric cross-match) according to our transplantation protocol. Low-risk patients had not received induction therapy. Standard-risk patients were administered induction therapy with ATG (ATG Fresenius, 2-5 mg/kg intravenously daily for 5–15 doses; Neovii-Biotech, Germany), and high-risk patients were administered induction therapy with ATG and basiliximab (Simulect, 20 mg intravenously day 0 and day 4; Novartis, Basel, Switzerland). The ATG dose was adjusted according to the number of platelets and leukocytes.

The maintenance immunosuppressive treatments included tacrolimus, mycophenolic acid derivatives, and steroids.





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**Table 1.** Demographic characteristics of patients according to induction groups.

| | Low-risk group (n=107) | Standard-risk group (n=104) | High-risk group (n=46) | p |
|---|---|---|---|---|
| Mean age (years) | 38±13.3 | 45±12.5 | 42±12.2 | 0.001 |
| Number of HLA mismatches | 2.8±2.6 | 2.8±1 | 1.6±0.9 | >0.05 |
| Type of donor (n) | | | | 0.001 |
| Living | 103 | 3 | 0 | |
| Deceased | 4 | 101 | 46 | |
| Sex (n) | | | | 0.001 |
| Female | 30 (28%) | 53 (50.9%) | 26 (56.5%) | |
| Male | 77 (72%) | 51 (49.1%) | 20 (43.5%) | |
| Etiology of CKD (n) | | | | |
| Hypertensive nephrosclerosis | 15 | 25 | 5 | 0.024 |
| Diabetic nephropathy | 7 | – | – | <0.001 |
| Glomerulonephritis | 31 | 27 | 16 | <0.001 |
| CAKUT | 13 | 13 | 9 | <0.001 |
| Others | 41 | 37 | 13 | <0.001 |
| Follow-up (months) | 24±9 | 71±37 | 48±36 | 0.001 |
| Duration of Dialysis (months) | 26±40 | 103±48 | 127±77 | 0.001 |

CKD – chronic kidney disease, CAKUT – congenital anomalies of the kidney and urinary tract.

Oral tacrolimus was initiated 2 days before transplantation (0.15 mg/kg body weight per day divided into 2 doses), and the dosage was adjusted to attain blood levels of 10–15 ng/mL for the first 3 months, then 5–10 ng/ml. Tacrolimus blood levels were assessed 2 times per week during the first 3 weeks of transplantation. Mycophenolate mofetil was given at 1000 mg twice a day, and methylprednisolone was administered at a dosage of 250 mg 4 times daily and 500 mg intraoperatively. On the first day after transplantation, 120 mg/day was given and then tapered to 10 mg/day at the end of the first month. All patients received CMV prophylaxis with valganciclovir during the first 3 months and Pneumocystis Jirovecii prophylaxis with trimethoprim-sulfamethoxazole for 1 year.

**Outcomes**

The primary endpoint was the onset of CMV disease or biopsy-confirmed BKV nephropathy. The secondary endpoints were biopsy-proven rejection episodes, graft loss, loss to follow-up or death.

CMV testing was performed at 3, 6, 12, and 24 months after transplantation and also as indicated. Polymerase chain reaction (PCR) was used for CMV detection. We used screening protocols for early detection and prevention of symptomatic BKV nephropathy by measuring BKV-DNA PCR in plasma at 1, 6, 12, and 24 months after transplantation. BKV nephropathy was confirmed by typical pathological findings and positive simian virus 40 T immunohistochemistry. CMV and BKV PCR testing was performed in a microbiology laboratory according to our transplantation protocol.

Rejection was considered to be the presence of allograft dysfunction and exclusion of other etiologies for graft dysfunction. This was subsequently confirmed by allograft biopsy and evaluated according to Banff criteria.

**Statistical analysis**

Description of patient baseline characteristics was performed through percentage for qualitative variables. For quantitative variables with normal distribution, mean standard deviation was used. For variables not following normal distribution mean, percentiles were used. The chi-square test was performed for qualitative variables, whereas the Mann-Whitney U test was used for qualitative variables with parametric distribution. Univariate survival comparisons were made by using the log-rank test. Patient and graft survival were analyzed by the Kaplan-Meier method and this duration for each patient was computed from baseline evaluation to the last follow-up. Logistic regression





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**Table 2.** Complications according to induction groups.

| | Low-risk group (n=107) | Standard-risk group (n=104) | High-risk group (n=46) | p |
|---|---|---|---|---|
| Viral complications | | | | |
| *Cytomegalovirus* disease | **4 (3.9%)** | **19 (21.1%)** | **8 (17.4%)** | **0.001** |
| BK virus nephropathy | 9 (8.5%) | 3 (2.9%) | 1 (2.2%) | >0.05 |
| Other Complications | | | | |
| Graft loss | **2 (1.9%)** | **17 (16.3%)** | **5 (10.9%)** | **0.001** |
| Patient loss | **0** | **14 (13.5%)** | **2 (4.3%)** | **0.001** |
| Rejection | 11 (14.3%) | 9 (8.7%) | 8 (17.4%) | >0.05 |

**Table 3.** The association between risk groups and development of CMV disease as described by logistic regression analysis.

| | Odds ratio | Confidence interval | p |
|---|---|---|---|
| Patient loss | 0.944 | 0.166–5.370 | 0.948 |
| Graft failure | 0.597 | 0.101–3.538 | 0.570 |
| Cardiovascular disease | 0.832 | 0.162–4.270 | 0.826 |
| ATG dosage | 1.239 | 0.672–2.285 | 0.492 |
| Rejection episodes | **3.400** | **1.020–11.335** | **0.046** |
| BKV nephropathy | 5.930 | 0.727–48.354 | 0.096 |

**Table 4.** The association between risk groups and development of BKV nephropathy as described by logistic regression analysis.

| | Odds ratio | Confidence interval | p |
|---|---|---|---|
| Patient loss | 0.390 | 0.036–4.224 | 0.438 |
| Cardiovascular disease | 1.062 | 0.204–5.514 | 0.943 |
| Rejection episodes | **4.386** | **1.199–16.041** | **0.025** |
| CMV disease | 0.144 | 0.017–1.212 | 0.075 |
| ATG dosage | 1.000 | 0.999–1.001 | 0.928 |

analysis was used to identify graft survival, patient loss, BKV nephropathy, CMV viremia, and the associated risk in terms of OR and 95% CIs. Variables were selected by backward elimination using likelihood ratio tests. All tests were two-tailed, and a P value of less than 0.05 was considered significant.

## Results

### Study population

We followed up 257 patients (148 male, 109 female) for a median of 55.5 (IQR 18–109.5) months. Demographic characteristics of patients according to induction groups are shown in Table 1. There were 107 low-risk patients who did not receive induction therapy, 104 standard-risk patients received a median of 710 mg (IQR 495–1267) ATG induction for 7 days (IQR 5–12), and 46 high-risk patients were administered 840 mg (IQR 500–1413) ATG induction for 8 days (IQR 6–16).

### Viral complications

CMV disease occurred in 4 low-risk patients (3.9%), 19 standard-risk patients (21.1%), and 8 high-risk (17.4%) patients. CMV disease incidence was significantly higher in the only ATG group compared to the group without induction treatment ($p<0.001$). Complications according to induction groups were shown in Table 2. In logistic regression analysis, CMV disease (OR, 3.400; 95% CI, 1.020 to 11.335; p=0.046) was an independent risk factor for allograft rejection.





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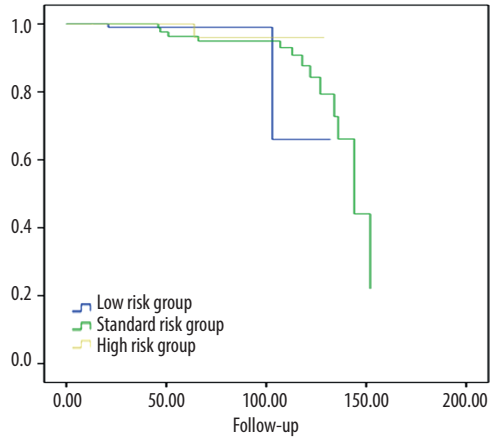


**Figure 2.** Patient survival analysis according to immunological risk groups.

Among 9 patients (8.3%) who had not received induction therapy, only 3 patients (2.9%) in the ATG group and 1 patient (2.2%) in the ATG and basiliximab group developed BKV nephropathy during follow-up. There was no significant difference in the incidence of BKV nephropathy among groups (p>0.05). Logistic regression analysis showed that BKV nephropathy was an independent risk factor for rejection episodes (OR, 4.386; 95% CI 1.199 to 16.041; p=0.025) (Tables 3, 4).

### Death and graft loss

Sixteen patients died during the follow-up period. Logistic regression analysis revealed that the dosage of ATG was an independent risk factor for death (OR, 10.685; 95% CI, 1.343 to 85.009; P=0.025), and Kaplan-Meier analysis showed that there were no significant differences in patient or graft survival among the 3 induction groups (p=0.518 and 0.587, respectively) (Figure 2, Tables 5, 6).

## Discussion

There were 107 low-risk patients who did not receive induction therapy, whereas 104 standard-risk patients received median 710 mg ATG induction for 7 days and 46 high-risk patients were administered 840 mg AT G induction for 8 days. CMV disease occurred in 4 low-risk patients, 19 standard-risk patients, and 8 high-risk patients. Among 9 patients who had not received induction therapy, only 3 patients in the ATG group and 1 patient in the ATG and basiliximab group developed BKV nephropathy. Logistic regression analysis revealed that the dosage of ATG was an independent risk factor for death.

The relationship between ATG usage and CMV infection is well known. This effect can be explained by stimulating the cellular nuclear factor-kB and viral replication by binding of nuclear factor-kB to the promoter region of the CMV immediate early antigen gene [10–15]. However, this effect does not occur when ATG is used as induction therapy with CMV prophylaxis [11].

**Table 5.** The association between risk groups and patient survival as described by logistic regression analysis.

| | Odds ratio | Confidence interval | p |
|---|---|---|---|
| ATG dosage | **10.685** | **1.343–85.009** | **0.025** |
| CMV disease | 0.848 | 0.148–4.849 | 0.853 |
| Number of HLA mismatches | 1.615 | 0.863–3.022 | 0.134 |
| Duration of hemodialysis | 0.998 | 0.984–1.012 | 0.801 |
| Rejection episodes | 0.750 | 0.075–7.460 | 0.806 |

**Table 6.** The association between risk groups and allograft survival as described by logistic regression analysis.

| | Odds ratio | Confidence interval | p |
|---|---|---|---|
| ATG dosage | 2.974 | 0.864–10.240 | 0.084 |
| CMV disease | 0.883 | 0.148–5.281 | 0.891 |
| Number of HLA mismatch | 0.876 | 0.437–1.754 | 0.708 |
| Rejection episodes | **8.504** | **1.826–39.605** | **0.006** |
| BKV nephropathy | 0.598 | 0.056–6.342 | 0.669 |





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According to our study, the frequency of CMV infection is increased in the ATG groups compared to the non-induction group, but this effect could not be demonstrated in logistic regression analysis. Higher CMV seropositivity and strong protection of CMV prophylaxis in these groups and the different effects of various ATG preparations can explain this effect.

The impact of induction regimens on BKV nephropathy is unclear and mostly based on database information [8–11]. Overall immunosuppression is more important in the development of BKV nephropathy than the specific drug [12]. Interestingly, we found less BKV nephropathy in the high immunologic risk group compared to the other 2 groups. This result may be related to the high mortality rate in these groups.

Previous studies demonstrated that reducing immunosuppression in BKV nephropathy is the mainstay of therapy, and lowering the immunosuppression is associated with low graft loss rates associated with BKV nephropathy. However, the early reduction of immunosuppression is associated with increased rejection. Our data showed that BKV nephropathy is an independent risk factor for rejection episodes.

Long-term usage of ATG is one of the main causes of morbidity and mortality in kidney transplant recipients. This effect is more prominent in allogeneic bone marrow transplantation patients treated with a higher dosage of ATG [13]. Similarly, we showed a significant relationship between ATG dosages and mortality rate.

Previous studies demonstrated that allograft rejection in different induction regimens appears to be similar, but higher doses of ATG are thought to be associated with an increased risk of death and infection [14–18]. Our study showed higher rejection episodes in the non-induction group compared to the other groups, but this difference was not statistically significant, and the dosage of ATG did not affect allograft survival.

Our study has some limitations. Firstly, this retrospective study only allowed us to assess associations and not prove causation. As in all retrospective studies, it is possible to confuse variables that are not considered in our analysis. Second, this was a single-center study, and some results may be specific to the center.

## Conclusions

This study demonstrated that the use of ATG as an induction therapy is associated with increased risk of death. In patients who will be treated with ATG as induction therapy, reducing the dose may be a rational strategy. In addition, prospective studies are needed to investigate the effect of induction therapies on CMV and BKV infections.

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