Epidemiology and Outcomes of Early-onset and Late-onset Adenovirus Infections in Kidney Transplant Recipients

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Abstract

Background: Adenovirus (ADV) infection after kidney transplantation (KT) causes significant morbidity. Patient characteristics and outcomes of ADV infection in KT recipients were investigated.

Methods: All adult KT recipients with ADV infection between January 2015 and June 2019 were included. ADV infection/disease was defined as detection of ADV DNA in clinical specimens/plus symptoms. Clinical and laboratory findings, treatments, and outcomes were assessed.

Results: ADV infection was diagnosed in 24/751 KT recipients (3.2%). Twenty (83%) were male with a median age of 47 years (IQR 36–58). Fifteen (63%) underwent deceased donor KT, and 13 (54%) received induction therapy. Twenty-one (88%) and four (17%) patients developed hemorrhagic cystitis and disseminated disease, respectively. There were equal distributions of early-onset (EOI) (≤ 3 months) and late-onset (LOI) (> 3 months) infections. Patients who were diagnosed with EOI had lower median absolute lymphocyte counts compared to those with LOI (735/mm³ [IQR 543–1123] vs. 1122/mm³ [IQR 784–1344], p = 0.04). All achieved resolution after reduction of their immunosuppression regimen and 13 (54%) received cidofovir therapy. Eighteen (75%) developed allograft dysfunction, of which 67% were transient. One (4%) underwent nephrectomy for allograft failure and 1 (4%) died (non-ADV-related). Patients with EOI were more likely to receive cidofovir therapy (75% vs. 33%, p = 0.04) and develop other opportunistic infections (75% vs. 8%, p < 0.001).
**Conclusions:** ADV infection after KT typically involves a genitourinary system and transiently impairs an allograft function. Those who developed early infection tend to have more lymphopenia, co-infection and receiving antiviral therapy.

**Keywords:** absolute lymphocyte count, cidofovir, cytomegalovirus, hemorrhagic cystitis, human adenovirus, lymphopenia
INTRODUCTION

Adenovirus (ADV) is a non-enveloped double-stranded DNA virus that can cause a wide variety of clinical symptoms in humans. ADV infection is usually asymptomatic or mild in immunocompetent individuals, but it can cause substantial morbidity in immunocompromised individuals (1). In kidney transplant (KT) patients, ADV can cause localized and invasive end-organ diseases including hemorrhagic cystitis, nephritis, pneumonitis, hepatitis, and gastroenteritis, which occasionally result in severe disseminated infection affecting multiple organs (2). Only a few published reports mention the epidemiology of ADV infection in adult KT recipients. Our team retrospectively reviewed the incidence of ADV infection in adult KT recipients, and it was approximately 4.9% (3, 4). As well as clinical and histopathological findings, nucleic acid amplification testing (NAAT) has been utilized for the diagnosis and monitoring of ADV infection after KT (2). Virus-specific immune monitoring has recently been explored in the management of solid organ transplant (SOT) recipients (5, 6). A low absolute lymphocyte count (ALC) is one risk factor associated with early ADV infection resulting in significant morbidity after KT (3). In a recent study, the restoration of ALC and ADV-specific T-cell immunity was correlated with viral clearance in KT recipients (7). The management of ADV infection in SOT recipients mainly involves the reduction of their immunosuppression regimen combined with cidofovir therapy. For the last few years, NAAT and cidofovir have been more accessible at our transplant center. In the present study, we investigated the incidence of ADV infection after KT, aspects of its epidemiology, diagnosis, and
management, and patient outcomes during the study period. Severe or disseminated ADV infection can require cidofovir therapy, but clinicians may hesitate to administer it to KT recipients in view of potential drug-related nephrotoxicity. Herein we report our experiences in the management of ADV infection in KT recipients using cidofovir, in terms of clinical and virological resolutions, adverse reactions, allograft outcomes, and rates of rejection after therapy.
METHODS

All adult KT recipients diagnosed with ADV infection between January 2015 and June 2019 at a single transplant center in Bangkok, Thailand were included in the present study. At our center, trimethoprim/sulfamethoxazole for pneumocystis prophylaxis, acyclovir for herpes simplex virus prophylaxis, and isoniazid for latent tuberculous infection therapy (regardless of status) were prescribed in all patients. Surveillance testing for cytomegalovirus (CMV) infection was performed due to a high prevalence of CMV-seropositive recipients except for those requiring anti-thymocyte globulin induction therapy when (val)ganciclovir prophylaxis was implemented. Instead, surveillance for ADV infection was not routinely performed. Only patients clinically suspected of ADV infection or exhibiting a consistent etiology underwent investigation, and other pathogens that were potentially responsible for their symptoms were excluded in the patients included in the study. ADV infection was defined as detection of ADV by NAAT in plasma or organ-specific specimens. ADV disease was defined as ADV infection combined with at least one specific organ symptom. Disseminated ADV disease was defined as ADV disease with the involvement of at least two specific organs. Early (EOI) and late (LOI) onset ADV infection was defined as the occurrence within and after 3 months, respectively. ADV DNA loads in plasma and urine specimens were measured via quantitative real-time polymerase chain reaction (PCR) assays (Adenovirus R-Gene® US Real-Time PCR kit, bioMérieux, Marcy l’Etoile, France from January 2015 until August 2018, and Adenovirus ELItE MGB® Kit, ELITech Group SpA, Turin, Italy thereafter). ADV DNA load was reported as log10 copies/mL with limits of quantification of 2.0–6.0 log10 copies/mL for the R-Gene® kit and 2.4–6.0 log10 copies/mL for the ELItE MGB® kit. ADV
DNA in respiratory specimens was measured via qualitative PCR assays (xTAG® Respiratory Viral Panel, Luminex Corporation, Austin, TX, USA). Imaging and histopathologic analyses were performed as appropriate based on clinical indications. Plasma ADV DNA loads were determined at the time of diagnosis and twice-weekly after treatment until no ADV DNA load was detected in two consecutive tests. Clinical resolution was defined as resolution of all symptoms. Virological resolution was defined as undetectable ADV DNA load in plasma or urine on two consecutive occasions.

Demographic, clinical, laboratory, and virological data pertaining to all patients were recorded, as were treatment details. Intravenous (IV) cidofovir at a dose of 5 mg/kg, 1 mg/kg three times weekly, or 0.5 mg/kg three times weekly (those with creatinine clearance < 50 mL/min) and IV immunoglobulin (IVIG) therapy at doses ranging from 0.5–2.0 g/kg was prescribed based on current guidelines (8). Outcomes were recorded, including clinical and virological resolution, patient survival, allograft function, and opportunistic infection other than ADV. Allograft function was calculated as the estimated glomerular filtration rate as determined via either the Cockcroft-Gault Formula, the Modification of Diet in Renal Disease Study Equation, or the Chronic Kidney Disease Epidemiology Collaboration equation. Transient allograft dysfunction was defined as any estimated glomerular filtration rate (eGFR) reduction compared to baseline that subsequently returned to baseline after the resolution of infection. Allograft failure and loss was defined as an irreversible estimated glomerular filtration rate reduction of > 50% from baseline, where “irreversible” was defined as reduction requiring chronic hemodialysis and/or re-transplantation. The Institutional Review Board of the Faculty of
Medicine of Ramathibodi Hospital, Mahidol University, Bangkok, Thailand approved the study protocol and waived the requirement to obtain any informed consent.

**Statistical analyses**

Patient demographic data and clinical characteristics were assessed via descriptive analysis. Categorical data were described as absolute and relative frequencies, and continuous data were described as medians with interquartile ranges (IQRs). Clinical and laboratory findings, treatments, and outcomes in those with EOI and LOI were compared via the Mann-Whitney U test and chi-square test for continuous and categorical data, respectively. \( p \) values < 0.05 determined via a two-tailed test were considered statistically significant. Statistical analyses were performed with Stata statistical software (version 15, StataCorp, LLC, College Station, TX, USA).
RESULTS

Epidemiology and demographic data

During the study period 751 KTs were performed at our transplant center, and of these, 24 (3.2%) patients were subsequently diagnosed with ADV infection. Each and overall patient characteristics are shown in Table 1 & 2, respectively. Twenty (83%) patients were male and the median age was 47 years (IQR 36–58 years). Twenty-three (96%) patients received their first KT, and 15 patients (63%) received an allograft from a deceased donor. The most common etiology of end-stage renal disease was unknown (67%). Thirteen patients (54%) received induction therapy, including 12 (50%) who received anti-thymocyte globulin (ATG) and 1 (4%) who received interleukin-2 receptor antagonist. The majority was followed by maintenance therapy including tacrolimus (75%), mycophenolate mofetil (83%), and prednisolone (100%). All donors and recipients were seropositive for CMV, hence preemptive CMV monitoring was undertaken after KT in the majority of cases. One patient underwent a second KT requiring ATG induction therapy and received IV ganciclovir prophylaxis during admission, and was subsequently switched to preemptive approaches for 3 months after KT. Trimethoprim/sulfamethoxazole for pneumocystis prophylaxis, acyclovir for herpes simplex virus prophylaxis, and isoniazid for latent tuberculous infection therapy were prescribed in all patients.

Diagnosis of adenovirus infection

The distribution of ADV infection onset after KT included 7 (29%) patients who developed infection within 1 month after KT, 5 (21%) between 1 and 3 months, and 12
(50%) after 1 year. There were equal distributions of patients diagnosed with EOI and LOI. Seven (29%) and 17 (71%) patients developed infection during a wet season (June to October) and a dry season (November to May), respectively. Among 7 patients (no respiratory symptoms) underwent an investigation for possible route of acquisition, nasopharyngeal (NP) swab for ADV PCR was detectable in two (29%) patients. Among LOI group, there was no patients developed rejection within 3 months prior to ADV infection.

The infections were classified as asymptomatic ADV (4%), ADV disease (4%), hemorrhagic cystitis (88%), upper respiratory tract infection (4%), lower respiratory tract infection (8%), gastroenteritis (4%), hepatitis (8%), interstitial nephritis (8%), epididymo-orchitis (8%), and disseminated disease (17%). Initial presentations included dysuria (83%), gross hematuria (83%), fever (46%), sore throat/runny nose (4%), shortness of breath (8%), reduced allograft function (8%), and testicular pain (8%). Urinalysis results included pyuria \( n = 7 \), microscopic hematuria \( n = 8 \), and proteinuria \( n = 10 \). Twenty-two (92%) patients had a detectable plasma ADV DNA load. Among those, the median initial plasma ADV load was 5.3 log copies/mL (IQR 3.5–6.0 log copies/mL), then it increased to a median peak plasma ADV load of 5.5 log copies/mL (IQR 5.3–6.0 log copies/mL). Twenty (83%) patients had detectable ADV DNA in urine and the majority (85%) had a urine ADV load of 6.0 log copies/mL or more. Two (17%) had detectable ADV DNA in respiratory specimens. At diagnosis the median total white blood cell count was 6255/mm\(^3\) (IQR 4208–10498/mm\(^3\)) and the median ALC was 883/mm\(^3\) (IQR 704–1398/mm\(^3\)). Probable ADV pneumonitis was diagnosed via the detection of ADV DNA from bronchoalveolar lavage fluid via PCR, histopathology revealed no viral cytopathic
change, and ADV *in situ* hybridization was not detected. ADV interstitial nephritis was defined as the detection of viral cytopathic changes in tubular cells, and ADV *in situ* hybridization was detected in one patient (proven) and in another it was inconclusive. In 2 patients, a diagnosis of probable epididymo-orchitis was supported by compatible symptoms, Doppler ultrasonography and detectable ADV DNA in urine without histopathological confirmation which was deemed to be invasive. Clinical, radiological, and histopathological findings of representative patients who were diagnosed with hemorrhagic cystitis, pneumonitis, epididymo-orchitis, and interstitial nephritis are shown in Figure 1.

Patients who were diagnosed with LOI were slightly more frequent to present with hemorrhagic cystitis compared to EOI (100% vs. 75%, *p* = 0.06). Patients who were diagnosed with EOI were more likely to be febrile, compared to those with LOI but this was not statistically significant (83% vs. 58%, *p* = 0.18). Patients with EOI had lower median absolute lymphocyte counts (ALCs) than those with LOI (735/mm³ [IQR 543–1123] vs. 1122/mm³ [IQR 784–1344], *p* = 0.04). There was no different in median peak plasma and urine ADV DNA load between two groups.

**Management**

After diagnosis the immunosuppression regimen was reduced in all patients. Mycophenolic acid was discontinued. The median dose reduction of mycophenolate mofetil was 1.5 g (IQR 1.25–1.50 g). Calcineurin inhibitors (CNI) were reduced to maintained trough levels of 3–5 ng/mL in patients who were on tacrolimus and 50–100 ng/mL in patients who were on cyclosporine. Prednisolone was
maintained as tolerated, to a median dose of 7.5 mg/day (IQR 5–15 mg/day). Thirteen (54%) patients received IV cidofovir with pre-hydration and post-hydration with 1 L of 0.9% normal saline solution, and of those patients 10 (77%) received oral probenecid with dosing of a total of 4 g oral probenecid; 2 g three hours prior to infusion, 1 g two hours after infusion, and 1 g eight hours after infusion. The details of cidofovir dosing are shown in Table 1. Five patients received weekly IV cidofovir at a dose of 5 mg/kg, 5 patients received 1 mg/kg three times weekly, and 3 patients received 0.5 mg/kg three times weekly (those with creatinine clearance < 50 mL/min), in most cases for 2 consecutive weeks followed by every other week until clinical and viral clearance. Different doses of cidofovir was selected on clinician preference based on the doses which were recommended by an international guideline. Patients diagnosed with EOI were more likely to receive IV cidofovir therapy (75% vs. 33%, $p = 0.04$) compared to those who diagnosed with LOI. Among 13 patients who received IV cidofovir, the creatinine increased in 9 (69%) patients after therapy and 5 (38%) returned to baseline. Allograft dysfunction occurred more frequently in patients who received IV cidofovir therapy compared to those withheld from therapy (38% vs. 18%, $p = 0.66$) as well as those received once weekly (40%) compared to thrice-weekly regimen (40% vs. 25%, $p = 0.57$), though the trends were not statistically significant. No patients developed uveitis, significant neutropenia, anemia, or proteinuria, or adverse reactions to probenecid including fever, rash, headache, or nausea.

Six (25%) patients received IVIG at doses ranging from 0.5–2.0 g/kg as adjunctive therapy. After resolution all patients were gradually restarted on mycophenolic acid to
baseline dosing. CNI was kept as appropriate trough level and low dose prednisolone was maintained.

**Outcome**

In all patients the median time from diagnosis to clinical resolution of 9 days (IQR 5–13 days) was significantly shorter than virological resolution of 46 days (IQR 30–60 days) \( (p < 0.001) \). Infection completely resolved without complications in 23 patients (96%). One patient was diagnosed with probable ADV pneumonitis that was subsequently complicated by organizing pneumonia requiring a tapered course of prednisolone therapy. Recurrence with low-level ADV DNAemia that was not clinically significant occurred in 1 patient (4%) after the resumption of immunosuppressant. Ten patients (42%) developed opportunistic infections other than ADV, including CMV (including asymptomatic CMV infection) \( (n=6) \), CMV syndrome \( (n=1) \), BK polyomavirus-associated nephropathy \( (n=2) \), human parainfluenza virus upper respiratory tract infection \( (n=1) \), urinary tract infection with *Enterococcus* spp. \( (n=1) \), *Escherichia coli* \( (n=1) \), and extended-spectrum beta-lactamase-producing *E. coli* \( (n=1) \). Patients diagnosed with EOI were more likely to develop opportunistic infection other than ADV (75% vs. 8%, \( p < 0.001 \)) including CMV co-infection (50% vs. 8%, \( p = 0.03 \)) compared to those diagnosed with LOI.

Eighteen (75%) patients developed allograft dysfunction, and of these 67% were transient. Three (13%) patients developed acute T-cell-mediated allograft rejection after therapy, and one (4%) of them developed concurrent antibody-mediated rejection. One
patient (4%) underwent nephrectomy for allograft failure and one (4%) died from a non-ADV-related cause.
DISCUSSION

Herein we have reported the most recent and comprehensive data on the epidemiology, clinical characteristics, management, and outcomes of ADV infection in KT recipients from a retrospectively analyzed cohort at a single transplant center. The genitourinary tract was the most commonly involved system, followed by some unusual presentations rarely seen in clinical practice. NAAT with or without histopathological testing is the main diagnostic tool used to achieve a diagnosis. Patients who developed ADV infection early post-transplant seems to have more lymphopenia at diagnosis, opportunistic infection other than ADV and receiving cidofovir therapy. While reduction of the immunosuppression regimen combined with IV cidofovir can evidently achieve a favorable clinical and virological outcome, transient allograft dysfunction remains a substantial consideration.

KT recipients have been considered to be at low to moderate risk of ADV infection compared to those who undergo liver or thoracic organ transplantation, likely due to less intense immunosuppression (9). A large cohort study of KT performed previously at our center provided an opportunity to investigate this uncommon infection after KT. The prevalence of ADV infection in KT recipients were slightly decreased during two periods of time approximately a decade apart, 4.9% from 2007 to 2010 (3) and 3.2% during the current study period of 2015 to 2019. Time to diagnosis varied similarly in the two studies, ranging widely from a few months to years after KT (3). Although ADV infection can occur all year round without seasonal variability. (10). The majority of ADV infection in our cohort occurred during a wet season. KT recipients with ADV infection can present with symptoms ranging from absent or mild to severe disseminated disease (8). The present
cohort was concordant with previous studies with regard to similar initial presentations and organ involvement of ADV infection with hemorrhagic cystitis in the majority of patients. Nanmoku et al.’s (11) recent report of a high incidence of ADV genitourinary tract infection (4.5%). In contrast we also detected uncommon presentations of ADV infection that are somewhat unique and specific to immunocompromised patients such as pneumonitis, epididymo-orchitis, and interstitial nephritis, due to the availability of NAAT and immunohistochemical testing at our institution. Clinicians who are managing these patients should be aware of. In the present study median initial and peak ADV loads were both > 5 log copies/mL, which is greater than they were in a previous study (3).

Observations in the present study were concordant with our previous study in which patients with early infection (onset within 3 months after KT) that was more severe tended to have lower ALCs at weeks 1 and 3 than patients with late infections (3). In the present cohort half of the patients developed ADV infection within 3 months post-KT, and these patients exhibited variable ALCs. Nierenberg et al. (12) reported that lymphopenia (< 500 cells/mm³) measured prior to transplantation is a potential tool for predicting opportunistic infection after liver transplantation. ALC indirectly represents impairment of non-specific cell-mediated immunity (CMI) in these patients. Our team recently reported low non-specific CMI as indicated by the total lymphocyte count and lymphocyte subset proportions (CD4+ and CD8+ T-cells), as well as ADV-specific CMI in patients diagnosed with ADV infection, then this immunity was later restored after resolution (7). Because there is no commercial assay available for measuring ADV-specific immunity in clinical practice, we encourage the use of a practical and simple tool to at least stratify and predict those who may develop severe infection.
Although no ideal management strategy for ADV infection has been established, in the present study all patients underwent reduction of their immunosuppression regimen as recommended in a current guideline (8), including discontinuation of mycophenolate, maintenance of low calcineurin inhibitor trough level, and the lowest dose of prednisolone tolerated (2). More than half of the patients received IV cidofovir compared to a quarter in a previous study (13), due to the recent increased availability of the medication at our institution. Cidofovir was considered to be cost-prohibitive in a resource-limited setting. Some patients were able to complete the induction phase but not the maintenance phase as recommended in the aforementioned guideline (8). Notably however, both early clinical and virological improvement in those patients would be less likely to require further treatment. The combination of an anti-ADV agent and optimized immunosuppression has been shown to improve clinical and virological outcomes, and although it takes approximately 2 months to achieve virological clearance the strategy reportedly facilitates more rapid clinical resolution. The present patients tolerated IV cidofovir well, without hematological or ocular toxicities. We found those received IV cidofovir were more likely to develop allograft dysfunction. However, the majority of the patients developed transient increases in serum creatinine known to be derived from multifactorial etiologies including cidofovir exposure, but the incidence of permanent damage in this context is reportedly low (14). Patients diagnosed with EOI were more likely to receive IV cidofovir therapy could be explained by more complexity of the infection during a period with more intense immunosuppression. We found less allograft dysfunction occurred in those received once-weekly compared to thrice-weekly regimen (40% vs. 25%) and a true explanation
for this different outcome has been elucidating. However, we did not observe other significant complications apart from nephrotoxicity in our cohort.

Although a few patients did not receive oral probenecid because a high urine drug concentration was achieved in order to treat ADV genitourinary tract infection, the allograft outcome was acceptable. This may have been due to aggressive IV saline hydration concomitantly with cidofovir therapy. Notably however, it is important to monitor renal function closely (including proteinuria) both before and during treatment.

Anti-ADV agents were implemented in the majority of the current patients who were diagnosed with ADV disease, facilitating evaluation of the efficacy of these agents. Cidofovir with and without IVIG has been reported to be effective in some SOT including KT recipients diagnosed with disseminated disease (15, 16). The true efficacy of cidofovir and/or IVIG is difficult to assess based on outcome however, because all patients underwent reduction of their immunosuppression regimen. Since there has been no randomized control trial of cidofovir and IVIG to support efficacy, a current guideline suggested considering those agents for severe or disseminated ADV disease and hypogammaglobulinemia, respectively. (8)

Apart from antiviral agents and adjunctive therapies, it has been reported that ADV-specific immunity is related to ADV clearance in KT recipients (5, 7). Allograft rejection may occur as a consequence of reduction of an immunosuppressive regimen. Therefore, one goal is to balance immunosuppression during infection and maintain the allograft by resuming immunosuppression as soon as the infection is controlled. A future study measuring specific ADV-specific immunity in order to facilitate optimal management in this setting is encouraged. Although KT recipients with disseminated disease are at a
high risk of mortality, in the present study there were no cases of disseminated disease-associated mortality. That was likely due to early diagnosis, prompt reduction of an immunosuppressive regimen, and vigilant management (6).

The current study had some limitations. There is an inherent possibility of bias due to the retrospective nature of the study. The true incidence of ADV infection was likely underestimated due to a lack of preemptive ADV load monitoring, which would have facilitated the diagnosis of asymptomatic ADV infection. Notably such preemptive ADV load monitoring is currently not advocated, and in Humar et al. (17) half of the patients developed transient and self-limiting reactivation without clinical significance. Accordingly, preemptive monitoring is not recommended in the aforementioned guidelines (8). Additionally, approximately one-third of patients had CMV co-infection, a sole effect of each pathogen which contributes the symptoms could be limited. An immunomodulatory effect of CMV infection is known to place patients at risk of infection from another opportunistic pathogen (18). Lastly, since the rarity of the disease which could limit a sample size, therefore an independent risk factors analyzed from multivariate analysis to investigate from this small cohort would not be allowed.

CONCLUSIONS

During recent years ADV has remained a relatively uncommon pathogen that can cause genitourinary tract infection in adult KT recipients. Low ALC at the time of diagnosis may predict an increased risk of ADV infection in KT recipients early post KT. Effective management is facilitated by early diagnosis assisted by readily available NAAT, supportive care, and reduction of immunosuppression. This combination can evidently
achieve favorable clinical and virological outcomes. Although transient worsening of allograft function may occur it is not associated with high mortality. 

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None.

CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest. All authors have submitted the ICMJE conflicts of interest form.

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FIGURE LEGENDS

Figure 1: Clinical, radiographic, and histopathology findings in kidney transplant recipients diagnosed with adenovirus infection. (A) Gross hematuria (B) Computed tomography of the chest showed newly developed patchy ground glass opacities with overlying consolidation opacity as well as several scattering solid nodules in both lungs (C) Doppler ultrasonography of the testes showed relatively enlarged size and increased vascularity of the right testis without mass or abnormal echogenicity. (D) Histopathology findings of the renal allograft biopsy showed lymphoplasmacytic infiltration in the interstitium with tubular injury and focal tubulitis. (PAS X 400).

TABLE LEGENDS

Table 1: Patient characteristics, management, and outcomes in 24 kidney transplant recipients diagnosed with adenovirus infection.

Table 2: Baseline characteristics of 24 kidney transplant recipients

Table 3: Clinical, laboratory, immunological, management, and outcome data derived from 24 kidney transplant recipients who were diagnosed with early and late onset ADV infection
| Patient | Age (years) | Sex | Type of KT | Induction regimen | Maintenance regimens | Onset after KT (months) | Diagnosis | Plasma/urine peak ADV DNA load (log copies/mL) | Cidofovir | IVIG | Clinical outcome / other infections | Allograft outcome | Survived |
|---------|-------------|-----|------------|-------------------|----------------------|------------------------|-----------|---------------------------------|-----------|------|---------------------------------|---------------|----------|
| 1       | 37          | M   | LRKT       | IL2RA             | TAC Everolimus Pred  | 0.50                   | ADV-associated hemorrhagic cystitis | 5.4 / > 6.0 | Yes, 3 mg/kg/wk (divided as three times a wk) at wk 0 without oral probenecid | Yes, 0.5 g/kg at week 1 | Resolved | Transient allograft dysfunction | Yes          |
| 2       | 45          | M   | DDKT       | IL2RA             | TAC MMF Pred         | 0.50                   | Disseminated ADV disease (hemorrhagic cystitis, right epididymo-orchitis) | > 6.0 / > 6.0 | Yes, 1.5–3.0 mg/kg/wk (divided as three times a wk) at wk 0,1 with oral probenecid | Yes, 2 g/kg (in 5 divided doses daily) | Resolved / asymptomatic CMV infection | Transient allograft dysfunction | Yes          |
| 3       | 38          | F   | DDKT       | IL2RA             | TAC MMF Pred         | 0.50                   | ADV-associated hemorrhagic cystitis | 4.2 / > 6.0 | Yes, 1.5–3.0 mg/kg/wk (divided as three times a wk) at wk 0,1 with oral probenecid | No | Resolved | Transient allograft dysfunction | Yes          |
| 4       | 58          | M   | LRKT       | IL2RA             | CsA MMF Pred         | 0.75                   | ADV-associated hemorrhagic cystitis | > 6.0 / > 6.0 | Yes, 5 mg/kg/wk at wk 0,1 with oral probenecid | No | Resolved / Asymptomatic CMV infection | Allograft dysfunction | Yes          |
|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 5 | 42 | M | LRKT | IL2RA | TAC | MMF | Pred | 1 | Asymptomatic ADV infection | 3.6 / 4.6 | No | No | Resolved / asymptomatic CMV infection | No allograft dysfunction | Yes |
| 6 | 34 | F | Re- | IL2RA | TAC | MMF | Pred | 1 | ADV-associated hemorrhagic cystitis, ADV interstitial nephritis | > 6.0 / > 6.0 | Yes, 1.5 mg/kg/wk (divided as three times a wk) at wk 0,1,2 with oral probencid | Yes, 2.8 g/kg (in 7 divided doses daily) | Resolved, human parainfluenza URI, E. coli UTI | Allograft failure, acute antibody-mediated and T-cell-mediated rejection / graft loss | Yes |
| 7 | 60 | M | None | IL2RA | CsA | MMF | Pred | 1 | ADV Pneumonitis | < LLOQ / not detected | No | No | Organizing pneumonia, resolved / Asymptomatic CMV infection | Transient allograft dysfunction | No (non-ADV-related) |
| 8 | 56 | M | None | IL2RA | CsA | MMF | Pred | 1.50 | ADV-associated hemorrhagic cystitis | 5.1 / > 6.0 | No | No | Resolved | Transient allograft dysfunction | Yes |
| 9 | 42 | M | LRKT | IL2RA | CsA | MMF | Pred | 1.50 | ADV-associated hemorrhagic cystitis | > 6.0 / > 6.0 | Yes, 5 mg/kg/wk at wk 0,1 without oral probencid | No | Resolved / ESBL-producing E. coli UTI | Allograft dysfunction, acute T-cell-mediated rejection | Yes |
| No. | Age | Sex | HLA-Typ | Other Immunosup | Disseminated ADV disease (hemorrhagic cystitis, left epididymo-orchitis, pneumonitis, hepatitis) | Disease Duration | Treatment 1 | Treatment 2 | Resolution | Allograft Dysfuction |
|-----|-----|-----|---------|-----------------|-----------------------------------------------------------------------------------------------|----------------|------------|-------------|------------|---------------------|
| 10  | 36  | M   | DDKT    | IL2RA TAC MMF Pred | > 6.0 / > 6.0                                                                                 | Yes, 3 mg/kg/wk (divided as three times a wk) at wk 0,1 with oral probenecid | Yes, 2 g/kg (in 5 divided doses daily) | Resolved / asymptomatic CMV infection | Yes |
| 11  | 59  | F   | DDKT    | IL2RA TAC MMF Pred | 5.7 / > 6.0                                                                                  | Yes, 5 mg/kg/wk at wk 0,1 with oral probenecid | No | Resolved / Enterococcus spp. UTI, BKVAN | Yes |
| 12  | 30  | M   | LRKT    | None CsA MMF Pred | 5.5 / N/A                                                                                   | Yes, 5 mg/kg/wk at wk 0, 1, 3, 5 with oral probenecid | No | Resolved / asymptomatic CMV infection | No |
| 13  | 53  | M   | DDKT    | IL2RA TAC MMF Pred | 5.4 / > 6.0                                                                                  | Yes, 3 mg/kg/wk (divided as three times a wk) at wk 0,1 without oral probenecid | Yes, 2 g/kg (in 5 divided doses daily) | Resolved | Allograft dysfunction | Yes |
| 14  | 55  | F   | DDKT    | None TAC MMF Pred  | > 6.0 / 5.0                                                                                  | Yes, 3 mg/kg/wk (divided as three times a wk) at wk 0, then 5 mg/kg/wk at wk 1, 3, 5 without oral probenecid | No | Resolved | No allograft dysfunction | Yes |
| Patient | Age | Gender | Donor Type | Rejection | Cause of Rejection | Treatment | Response | Resolution | Allograft Dysfunction | Conclusion |
|---------|-----|--------|------------|-----------|-------------------|-----------|---------|------------|----------------------|------------|
| 15      | 29  | M      | LRKT       | None      | Disseminated ADV disease (hemorrhagic cystitis, hepatitis) | > 6.0 / > 6.0 | Yes, 5 mg/kg/wk at wk 0,1 with oral probenecid | No         | Resolved             | Transient allograft dysfunction | Yes        |
| 16      | 43  | M      | DDKT       | None      | Disseminated ADV disease (hemorrhagic cystitis, gastroenteritis, upper respiratory tract infection) | 5.7 / > 6.0 | No         | Yes, 1 g/kg (in 3 divided doses daily) | Resolved / CMV syndrome, BKVAN | Transient allograft dysfunction | Yes        |
| 17      | 49  | M      | DDKT       | IL2RA     | ADV-associated hemorrhagic cystitis | < LLOQ / 5.6 | No         | No         | Resolved             | Transient allograft dysfunction | Yes        |
| 18      | 62  | M      | DDKT       | None      | ADV-associated hemorrhagic cystitis | 5.3 / > 6.0 | Yes, 3 mg/kg/wk (divided as three times a wk) at wk 0 with oral probenecid | No         | Resolved             | No allograft dysfunction | Yes        |
| 19      | 59  | M      | DDKT       | None      | ADV-associated hemorrhagic cystitis | > 6.0 / > 6.0 | No         | No         | Resolved             | Transient allograft dysfunction | Yes        |
| 20      | 54  | M      | DDKT       | IL2RA     | ADV-associated hemorrhagic cystitis | 5.0 / > 6.0 | No         | No         | Resolved             | Allograft dysfunction | Yes        |
| No | Age | Sex | Transplant Type | Immunosuppression | Duration | Laboratory Findings | Resolution | Rejection Type |
|----|-----|-----|-----------------|------------------|----------|-------------------|-----------|---------------|
| 21 | 57  | M   | DDKT            | None             | 40       | ADV-associated hemorrhagic cystitis > 6.0 / > 6.0 | No        | No            | Resolved      | No allograft dysfunction | Yes |
| 22 | 67  | M   | DDKT            | TAC, MMF, Pred   | 47       | ADV-associated hemorrhagic cystitis 3.9 / > 6.0 | No        | No            | Resolved      | Transient allograft dysfunction | Yes |
| 23 | 24  | M   | LRKT            | TAC, MMF, Pred   | 59       | ADV-associated hemorrhagic cystitis 5.1 / > 6.0 | No        | No            | Resolved      | Transient allograft dysfunction | Yes |
| 24 | 34  | M   | DDKT            | IL2RA            | 63       | ADV-associated hemorrhagic cystitis 5.3 / > 6.0 | No        | No            | Resolved      | Allograft dysfunction, acute T-cell mediated rejection | Yes |

ADV, adenovirus; ALC, absolute lymphocyte count; ATG, anti-thymocyte globulin; BKVAN, BK polyomavirus-associated nephropathy; CMV, cytomegalovirus; CsA, cyclosporine; DDKT, deceased-donor kidney transplantation; DNA, deoxyribonucleic acid; ESBL, extended-spectrum beta-lactamase; F, female; IL2RA, interleukin-2 receptor antagonist; IVIG, intravenous immunoglobulin; LLOQ, lower limit of quantification; M, male; MMF, mycophenolate mofetil; MPS, mycophenolate sodium; LRKT, living-related kidney transplantation; N/A, not applicable; Pred, prednisolone; TAC, tacrolimus; UTI, urinary tract infection
Table 2

| Characteristic, n (%)                                      | N =24 |
|-----------------------------------------------------------|-------|
| Age (median, IQR; years)                                  | 47 (36-58) |
| Male sex                                                 | 20 (83) |
| Etiologies of end-stage renal disease                     |       |
| - Diabetic nephropathy                                    | 2 (8) |
| - IgA nephritis                                          | 3 (13) |
| - Lupus nephritis                                        | 2 (8) |
| - Chronic glomerulonephritis                             | 1 (4) |
| - Unknown etiology                                       | 16 (67) |
| Deceased-donor kidney transplantation                    | 15 (63) |
| Immunosuppressive regimens                               |       |
| Induction therapy                                        |       |
| - None                                                    | 11 (46) |
| - Anti-thymocyte globulin                                 | 1 (4) |
| - Interleukin-2 receptor antagonist                       | 12 (50) |
| Maintenance therapy                                      |       |
| - Tacrolimus                                             | 18 (75) |
| - Cyclosporine                                           | 6 (25) |
| - Mycophenolate mofetil                                  | 20 (83) |
| - Mycophenolate sodium                                   | 3 (13) |
| - Everolimus                                             | 1 (4) |
| - Prednisolone                                           | 24 (100) |
ADV, adenovirus; IQR, interquartile range

**Table 3**

|                                | Early onset (n = 12) | Late onset (n = 12) | p value |
|--------------------------------|----------------------|---------------------|---------|
| **ADV infection, n (%)**       |                      |                     |         |
| - Asymptomatic infection       | 1 (8)                | 0                   | 0.30    |
| - Hemorrhagic cystitis         | 9 (75)               | 12 (100)            | 0.06    |
| - Interstitial nephritis       | 1 (8)                | 1 (8)               | >0.999  |
| - Hepatitis                    | 1 (8)                | 1 (8)               | >0.999  |
| - Upper respiratory tract infection | 0                   | 1 (8)               | 0.30    |
| - Pneumonitis                  | 2 (17)               | 0                   | 0.14    |
| - Gastroenteritis              | 0                    | 1 (8)               | 0.30    |
| - Epididymo-orchitis           | 2 (17)               | 0                   | 0.14    |
| - ADV syndrome                 | 1 (8)                | 0                   | 0.30    |
| - Disseminated infection       | 2 (17)               | 2 (17)              | >0.999  |
| **Clinical presentations, n (%)** |                      |                     |         |
| - Fever                        | 10 (83)              | 7 (58)              | 0.18    |
| - Dysuria                      | 9 (75)               | 11 (92)             | 0.27    |
| - Gross hematuria              | 9 (75)               | 11 (92)             | 0.27    |
| - Testicular pain              | 2 (17)               | 0                   | 0.14    |
| - Shortness of breath          | 2 (17)               | 0                   | 0.14    |
| **Laboratory findings at diagnosis, median (IQR)** | | |   |
| - Total white blood cell count (cells/mm³) | 7670 | 6050 | 0.37 |
### Absolute lymphocyte count (cells/mm$^3$)

|                | Median | IQR   |
|----------------|--------|-------|
| (4013-10658)   | 735    | (543-1122) |
| (4208-7423)   | 1122   | (784–1,344) |

### Peak urine ADV DNA load (log10 copies/mL)

|                | Median | IQR  |
|----------------|--------|------|
| (4013-10658)   | 6.0    | (6.0-6.0) |
| (4208-7423)   | 6      | (6.0-6.0) |

### Peak plasma ADV DNA load (log10 copies/mL)

|                | Median | IQR   |
|----------------|--------|-------|
| (4013-10658)   | 5.7    | (5.1-6.0) |
| (4208-7423)   | 5.4    | (5.1-6.0) |

### Treatment, n (%)

| Treatment                  | (4013-10658) | (4208-7423) |
|----------------------------|--------------|------------|
| Cidofovir                  | 9 (75)       | 4 (33)     |
| Intravenous immunoglobulin | 4 (25)       | 2 (17)     |

### Outcome, n (%)

| Outcome                                                                 | (4013-10658) | (4208-7423) |
|-------------------------------------------------------------------------|--------------|------------|
| Time to virological resolution (median, IQR; days)                     | 56 (35-60)   | 43 (28-52) |
| Time to clinical resolution (median, IQR; days)                        | 10 (5-17)    | 6 (5-11)   |
| Opportunistic infection other than ADV                                  | 9 (75)       | 1 (8)      |
| Cytomegalovirus co-infection                                            | 6 (50)       | 1 (8)      |
| Normal allograft function                                              | 3 (25)       | 3 (25)     |
| Transient allograft dysfunction                                        | 6 (50)       | 6 (50)     |
| Allograft dysfunction                                                  | 2 (17)       | 3 (25)     |
| Allograft failure                                                       | 1 (8)        | 0          |
| Acute T-cell-mediated rejection                                        | 2 (17)       | 1 (8)      |
| Antibody-mediated rejection                                            | 1 (8)        | 0          |
| Hemodialysis required after transplantation                             | 1 (8)        | 0          |
| Mortality (non-ADV-related)                                            | 1 (8)        | 0          |

ADV, adenovirus; DNA, deoxyribonucleic acid; IQR, interquartile range; RBC, red blood cell