

# Campath-1H Induction and the Incidence of Infectious Complications in Adult Renal Transplantation

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**Background.** The purpose of this study was to evaluate adult renal transplantation patients who received a alemtuzumab (Campath-1H)-based induction protocol for the incidence of infectious complications.

**Methods.** We began using 30 mg Campath-1H intravenously for induction therapy in May 2003. The patients were treated with a maintenance regimen of tacrolimus or mycophenolate mofetil (MMF), and rapidly tapered prednisone; valganciclovir was used for CMV prophylaxis. Forty-nine adult patients who received renal transplants between May 1, 2003 and June 7, 2004 were included. The mean follow-up time was 13.7 months with a range of 10-24 months. Data were collected via a retrospective chart review.

**Results.** The infectious complications noted in the Campath-1H group were compared with a historical group of 56 patients receiving conventional immunosuppression. There was one case of cytomegalovirus (CMV) viremia and two cases of CMV disease (one pneumonitis and one enteritis). There were four cases of urinary tract infection and one extremity cellulitis. One patient developed Cryptococcal meningitis. Eight of the 49 (16%) patients in the Campath group had an infectious complication, compared to 18 out of 56 (32%) in the historical group.

**Conclusion.** Campath-1H induction for renal transplantation appears to have a low incidence of associated infectious complications when compared to historical regimens.

**Keywords:** Campath-1H, Renal transplantation, Infection.

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Alemtuzumab (Campath-1H; ILEX, San Antonio, TX) is a humanized anti-CD52 lymphocytic antibody that is increasingly being used for induction immunosuppression. Several studies from large centers have demonstrated decreased rates of acute rejection and improvement in short-term graft survival (1–3). It has also been shown to be associated with a low rate of infectious complications (4–6). However, to our knowledge, a detailed analysis of the infectious complications associated with Campath-1H induction has not been reported in the literature.

The use of novel immunosuppressive agents has altered the spectrum of infections in transplant recipients. Recognition of the changing epidemiology of these opportunistic infections is vital for the clinical care of these patients to improve outcome and decrease morbidity. We undertook this study to analyze the total number of infectious complications

as well as the number of individual infectious episodes seen in renal transplant patients after Campath-1H induction. We compared these with historical controls in the same institution prior to the introduction of Campath-1H.

## MATERIALS AND METHODS

Campath-1H induction therapy was utilized in adult renal transplant recipients beginning in May 2003 with Institutional Review Board approval. Data was collected by retrospective chart review after Health Insurance Portability and Accountability Act approval of the study protocol. All adult renal transplants over the age of 18 years, performed at our institution between May 2003 and June 2004, were included in the study. Data was analyzed for total incidence of infectious complications and the type of infectious episodes. Statistical comparisons were made utilizing a chi-square test. *P* values <0.05 were considered statistically significant.

## Immunosuppressive Therapy

All patients received 30 mg of Campath-1H as a single dose given intravenously (IV) over 2 hours prior to reperfusion of the kidney. Before giving Campath-1H, all patients were premedicated with acetaminophen 650 mg per oral (PO), diphenhydramine 50 mg IV, and solumedrol 1 gm IV over 30 minutes. Ranitidine 50 mg IV was also given as gastrointestinal prophylaxis.

Maintenance immunosuppression consisted of tacroli-

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mus (Prograf; Fujisawa, Deerfield, IL), aiming for a goal trough level of 10 ng/ml, or mycophenolate mofetil (MMF; Cellcept, Roche, Nutley, NJ), 1 g PO twice daily. MMF was used in expanded criteria donors, nonheartbeating, donors and in the kidneys that experienced delayed graft function. Maintenance immunosuppression was started on postoperative day 1, and also consisted of prednisone 20 mg PO daily. This was weaned off postoperatively by 8 weeks (2.5 mg/week).

### Associated Therapy

All patients were given perioperative antibiotic prophylaxis with a first-generation cephalosporin (Ancef; 1 g IV q 8 hr × 6 doses). *Pneumocystis jirovecii* prophylaxis was with trimethoprim-sulfamethoxazole, (Bactrim SS; 1 PO every Monday, Wednesday, and Friday) for 6 months. Antifungal prophylaxis was with nystatin, swish and swallow 5 ml PO QID for 3 months. Valganciclovir (Valcyte, Roche, Nutley, NJ) 450–900 mg PO (dose adjusted to renal function) was used as cytomegalovirus (CMV) prophylaxis in all patients. For low-risk (donor negative/recipient negative for CMV) patients, the duration of prophylaxis was 3 months. For all other combinations, the duration of prophylaxis was 6 months.

### Follow-up

Patients were seen daily during the initial hospitalization, weekly for the next 2 months, and every 2–6 weeks thereafter until 1 year after transplantation. Protocol biopsies were performed at 2 weeks, 3 months, and 1 year, or as clinically indicated. Complete blood count (CBC), basic metabolic panel, and tacrolimus levels were checked weekly for the first month, and twice weekly thereafter. Liver function tests were drawn at first follow-up visit. CMV antigenemia was monitored twice monthly for the first 3 months and monthly thereafter for a total of 12 months. Screening for BK virus infection was performed on all patients by urine cytology at 1 year postoperatively. Quantitative serum BK virus PCR testing was done if urine cytology was positive for BK virus. Protocol allograft biopsies at 1 year posttransplant were also tested for BK virus nephropathy.

### Control Group

The infectious complications in the Campath-1H group were compared to a historical group of 56 patients transplanted prior to May 2003 at our center. The historical group received conventional immunosuppression with cyclosporine, MMF, and prednisone. Tacrolimus was not used

in our institution prior to May 2003, but we felt that the historical group, which still received a calcineurin inhibitor, would be a reasonable surrogate. In addition, 27 patients in the historical group also received two doses of basiliximab (Simulect; Novartis). Basiliximab was administered on the day of operation and on postoperative day 4 at a dose of 20 mg. Ganciclovir was used for CMV prophylaxis. These patients were not tested for BK virus nephropathy. Definitions of infectious complications are summarized in Table 1.

## RESULTS

Of the 49 kidney transplant recipients on our Campath-1H induction protocol, 15 were living donors and 34 were cadaveric recipients. Forty-four were first transplant recipients and five were retransplant recipients. Mean recipient age was 52.1 years (range, 18–72 years). Most of the recipients (98%) were white. There were 26 male patients and 23 female patients. Twenty-eight patients (57.1%) were low risk for CMV infection (donor negative/recipient negative), and 21 patients (42.9%) were high risk for CMV infection (Table 2). Patient survival was 92% and death-censored graft survival was 98% at one year (overall graft survival was 90%). There were four mortalities, three due to cardiac events and one from a motor vehicle accident. There was one graft loss from withdrawal of immunosuppression in a patient with life-threatening cryptococcal meningitis. There were eight total infectious complications. The incidence of infectious complications was 16% (Table 3). There were three urinary tract infections (6%), two cases of CMV disease (one pneumonitis and one enteritis; 4%), one case of CMV antigenemia (2%), one extremity cellulitis (2%), and one patient with cryptococcal meningitis (2%). No patients developed BK virus nephropathy or posttransplant lymphoproliferative disease. The timeline for development of infectious complications ranged from 44–400 days posttransplant.

### CMV Disease and Antigenemia

CMV disease was observed in a 59-year-old male recipient of a living donor renal transplant, 2 months after stopping a 6-month course of prophylactic valganciclovir. The patient was high risk for CMV (donor positive/recipient negative CMV status). His valganciclovir prophylaxis had been interrupted at the end of 3 months posttransplant for 5 weeks because of low white blood cell count requiring Neupogen therapy. He was also a zero antigen match with his donor. He was being maintained on tacrolimus monotherapy with a creatinine clearance of greater than 60. The patient developed

**TABLE 1.** Definitions of infectious complications

| Complication                | Definition  |
|-----------------------------|---|
| Cytomegalovirus antigenemia | More than 50 cells per 300,000 white blood cells on serum sample  |
| Cytomegalovirus disease     | Positive for cytomegalovirus antigenemia and clinical evidence of disease: fever, arthralgia, enteritis, pneumonitis, leukopenia, or tissue diagnosis |
| Urinary tract infection     | More than 10 <sup>5</sup> bacteria/mL in urine culture  |
| Bacteremia                  | Blood culture positive for bacteria with temperature >37.5°C  |
| Cryptococcal meningitis     | Positive cerebrospinal fluid culture  |
| Herpes zoster/simplex virus | Typical skin lesion or positive viral culture   |
| BK virus                    | Quantitative BK viremia in plasma, positive urine cytology and tissue biopsy  |

**TABLE 2.** Campath-1H induction protocol patient demographics

|                    | n    | %  |
|--------------------|------|----|
| Total patients     | 49   | —  |
| Mean age (years)   | 52.1 | —  |
| Median age (years) | 55   | —  |
| Male               | 26   | 53 |
| Female             | 23   | 47 |
| Living donor       | 15   | 31 |
| Cadaveric donor    | 34   | 69 |
| High-risk CMV      | 21   | 43 |
| Low-risk CMV       | 28   | 57 |
| First transplants  | 44   | 88 |
| Retransplants      | 5    | 12 |

**TABLE 3.** Incidence of infectious complications in the Campath-1H group

|                            | n | %  |
|----------------------------|---|----|
| Total number of infections | 8 | 16 |
| CMV disease                | 2 | 4  |
| CMV antigenemia            | 1 | 2  |
| Cryptococcal meningitis    | 1 | 2  |
| Urinary tract infection    | 3 | 6  |
| Extremity cellulitis       | 1 | 2  |

fever, malaise, arthralgia and diarrhea. CMV antigenemia was elevated to 1,140 cells/300,000 white blood cells (WBCs). He was restarted on valganciclovir 900 mg PO bid with resolution of his antigenemia, and future CMV antigenemia studies were consistently negative. Valganciclovir was continued for another 3 months.

The second patient who developed CMV disease was a 53-year-old female patient who received a living donor renal transplant. Her CMV status was donor positive/recipient positive, and she developed CMV pneumonitis (bronchoalveolar lavage culture positive) 2 months after her transplant. Her valganciclovir prophylaxis had been held previously for a low white cell count. She was treated with intravenous ganciclovir for 5 days with resolution of her CMV antigenemia 6 days from admission. She was then continued on oral valganciclovir for 3 months.

CMV antigenemia greater than 50 cells/300,000 WBCs was observed in a 39-year-old female recipient of a cadaver renal transplant, 5 months posttransplant. Her CMV status was high risk (donor positive/recipient negative). She was being maintained on tacrolimus monotherapy. Valganciclovir prophylaxis had been interrupted at 3 months because of low WBC count. She was restarted on valganciclovir with resolution of her CMV antigenemia, which peaked at 96 cells. She was never symptomatic and her creatinine clearance was >60.

Our definition of CMV antigenemia (50 cells/300,000 WBCs) was based on studies showing the highest positive predictive value and specificity in the development of symptomatic CMV infection using this criterion (14). Transient asymptomatic CMV antigenemia (<20 cells/300,000 WBCs) was observed in 11 patients from a time period ranging from

3–11 months posttransplant. No treatment was instituted and serial CMV antigenemia was monitored, with resolution of antigenemia over 2–4 weeks. Of interest, 12/49 patients had interruption of valganciclovir prophylaxis at some point in their course because of a low WBC count related to valganciclovir use or concurrent use of mycophenolate mofetil. Of these patients, three had CMV antigenemia >50/300,000 WBCs and eight patients had subclinical CMV antigenemia.

### Cryptococcal Meningitis

Cryptococcosis with meningitis was observed in a 65-year-old recipient of a cadaveric renal transplant 170 days posttransplant. The patient presented with headache and low-grade fever, after he had been painting the walls of his cold, damp basement. Cerebrospinal fluid examination was positive for cryptococcal antigen. Immunosuppressive therapy (tacrolimus) was discontinued and the patient was started on IV amphoterecin. A withdrawal of his immunosuppression resulted in graft loss and return to dialysis.

### Historical Comparison

In the historical group, the total incidence of infectious complications was 18/56 (32%). At that time routine surveillance of CMV antigen and BK virus was not being performed, so it is possible this number may have been higher. See Table 4 for types of infectious complications. As compared to the historical group (32%), the Campath-1H induction group (16%) had a lower rate of infectious complications, even though the *P* value was not statistically significant (*P*=0.061), as shown in Table 5.

### DISCUSSION

The frequency and use of induction therapy for renal transplantation has gradually been increasing over the last decade. A number of antilymphocytic agents are currently being used as induction agents (7). Although there have been no randomized trials of its use in transplantation in the United States, Campath-1H is increasingly being used in renal transplantation to induce profound lymphocyte depletion. Campath-1H was first used in renal transplantation by Calne at Cambridge University with excellent results (2). Since then, several centers in the United States have also used it with excellent short-term graft survival and with a decrease in the incidence of acute rejection (4, 8, 9). As immunosup-

**TABLE 4.** Infectious complications in Campath-1H group compared to a historical group

| Infectious complications | Campath-1H group | Historical group |
|--------------------------|------------------|------------------|
| n                        | 49               | 56               |
| CMV Disease              | 2                | 1                |
| CMV antigenemia          | 1                | 2                |
| Cryptococcal meningitis  | 1                | 0                |
| Bacteremia               | 0                | 2                |
| Cellulitis               | 1                | 1                |
| Urinary tract infection  | 3                | 8                |
| Herpes zoster            | 0                | 2                |
| Herpes simplex           | 0                | 3                |
| Total complications      | 8                | 18               |

**TABLE 5.** Incidence of infection: Campath-1H group vs. historical group

|                  | Total infectious complications | Incidence |
|------------------|--------------------------------|-----------|
| Campath-1H       | 8/49                           | 0.16      |
| Historical group | 18/56                          | 0.32      |

pressive agents and graft survival have improved, infectious complications have become a main obstacle to disease-free survival after organ transplantation. Evolving immunosuppressive regimens and the introduction of novel immunosuppressive agents has also altered the spectrum of infectious complications seen in renal transplantation (10). BK virus nephropathy, which in the past was seldom diagnosed, has increased in frequency. The presentation of opportunistic infections such as cytomegalovirus now occurs later in the post-transplant period.

In a descriptive analysis of transplant patients admitted from the emergency department, Trzeciak showed that infections were the most common indications for admission, with urinary tract infections and pneumonia being the most common (11). Dharnidarka and colleagues analyzed data from the North American Pediatric Renal Transplant Cooperative Study and concluded that posttransplant infections were the most common cause of hospitalization at all times up to 24 months posttransplant (12). The increased rates of hospitalization resulting from infections raises the concern that increased use of induction therapy might be a contributing factor.

Campath-1H causes profound lymphocyte depletion with T cells being suppressed the longest (up to 18–20 months). Our results show that in spite of this extended depletion, the rate of infectious complications, specifically those involving opportunistic infections, has remained low.

In conclusion, Campath-1H induction therapy in renal transplant recipients is associated with a low incidence of infectious complications as compared to a historical group. Irrespective of the use of prophylactic or preemptive therapy, close surveillance is essential because of the prolonged immunosuppressive effect of Campath-1H. Although follow up beyond 5 years will be required to evaluate our patients for late

complications, no patient in our study has developed post-transplant lymphoproliferative disease or malignancy to date.

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