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Infections after the use of alemtuzumab in solid organ transplant recipients: a comparative study

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Abstract

We undertook a retrospective cohort study comparing infection in solid organ transplant recipients receiving alemtuzumab (n = 726) versus basiliximab (n = 215) or antithymocyte globulin (ATG) (n = 85). Eighty-one percent of patients had kidney transplants. Overall, 33% of patients in the alemtuzumab group (240/724) developed infection compared with 40% (87/215) in the basiliximab group (odds ratio [OR], 0.72; 95% confidence interval [CI], 0.53–0.99; P = .04). The frequency of infection was similar in the alemtuzumab and ATG groups (33% versus 36%, respectively, P = .53). The frequency of fungal infections, most caused by *Candida* spp., was similar in the alemtuzumab and basiliximab groups (10% versus 9%); disseminated fungal infection occurred in 68% of the patients with fungal infection receiving alemtuzumab and in 30% of the patients with fungal infection receiving basiliximab (OR, 4.76; 95% CI, 1.58–14.28; P = .003). Basiliximab posed a higher risk than alemtuzumab for infection. Disseminated candidal infections were more common in patients receiving alemtuzumab.

Keywords: Alemtuzumab; Infection; Transplantation; Fungal; Bacterial; Viral

1. Introduction

Major advances in transplantation techniques and understanding of transplant biology have greatly improved the survival of renal transplant recipients. Each year, approximately 15 000 renal transplants are performed in the United States, with a 5-year survival exceeding 80% (http://www.unos.org [United Network for Organ Sharing, n.d.]). However, infection remains a major challenge in the solid organ transplant recipient and now exceeds rejection as the precipitating factor for hospitalization in patients in the first 2 years after a solid organ transplant (Dharnidharka et al., 2004).

In recent years, lymphocyte depletion has been used with increasing frequency as an induction strategy after transplantation and for treatment of rejection (Shapiro et al., 2005a, 2005b). Alemtuzumab (Campath-IH; Berlex, Montville, NJ) is a humanized monoclonal antibody directed against CD52, a cell surface antigen expressed on B and T lymphocytes, monocytes, and natural killer (NK) cells (Ferrajoli et al., 2001; Flynn and Byrd, 2000). It is a powerful cytolytic agent and is used therapeutically in bone marrow transplantation (Dumont, 2002; Hale, 2002) and several autoimmune diseases (Marsh and Gordon-Smith, 2001). Infusion of alemtuzumab results in marked decrement in circulating levels of NK cells, B cells, T lymphocytes, macrophages, and monocytes. Although numbers of NK cells, B cells, and monocytes typically return to normal levels within 3 to 6 months of alemtuzumab use, CD4+ and CD8+ T cells may remain low for years (Ferrajoli et al., 2001). In a trial of alemtuzumab in patients with rheumatoid arthritis, there was profound and persistent peripheral blood lymphopenia in the alemtuzumab-treated patients, affecting predominantly the CD4+ subset. Median CD4+ and CD8+ peripheral blood lymphocyte counts at 73 to 84 months after

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therapy were 185 and 95 cells/μL, respectively (Issacs et al., 2001). More recently, alemtuzumab has come into use for induction immunosuppression and treatment of rejection for solid organ transplantation in some transplantation centers (Gourishankar et al., 2002; Magliocca and Knechtle, 2006; Morris and Russell, 2006; Shapiro et al., 2005a, 2005b). Long-lasting lymphopenia has been confirmed in patients treated with alemtuzumab for induction of immunosuppression in solid organ transplantation administered maintenance mycophenolate mofetil or sirolimus in addition to calcineurin inhibitors (Knechtle et al., 2003, 2004).

Depletion of lymphocytes would be expected to result in an increased risk of opportunistic infections. Some series have found that alemtuzumab use was associated with an increase in the frequency of unusual infections (Abad et al., 2003; Magliocca and Knechtle, 2006; Martin et al., 2006; Nath et al., 2005; Silveira et al., 2007). However, others have not confirmed these findings (Barth et al., 2006), and thus, whether or not alemtuzumab use translates into an increased risk of infection in solid organ transplant recipients is unclear.

We performed a retrospective cohort study to determine the risk of infection in patients receiving alemtuzumab induction compared with basiliximab/daclizumab or antithymocyte/antilymphocyte globulin at time of transplantation. We focused particularly on fungal infections as the main outcome.

2. Methods

2.1. Sources of data

Using data from a prospectively maintained transplant database, supplemented by chart review and pharmacy billing records, we identified all 1738 patients who had undergone renal, liver, and kidney–pancreas transplantation at the University of Wisconsin, Madison, WI, between January 1, 2002, and December 31, 2005. For this retrospective cohort study, the cohort was constructed by including patients who received at least 1 dose of alemtuzumab as the alemtuzumab group. For retransplanted patients, only the first transplant was included. A comparator group was constructed by randomly selecting transplant recipients, using a random numbers table from a list of the transplant recipients who did not receive alemtuzumab but received basiliximab/daclizumab, antithymocyte globulin (ATG), and/or antilymphocyte globulin (OKT3). The study was approved by the institutional review board.

Data collection included demographics, information pertaining to transplantation, and infection. Relevant definitions are provided in Table 1. Definitions for fungal infections were adapted from Ascioglu et al. (2002).

All patients were given perioperative prophylaxis with cefazolin (renal transplants) and ceftriaxone (liver transplants). Selective digestive decontamination was not used. The alemtuzumab group received 1 (20 mg) or 2 doses (40 mg) of alemtuzumab intravenously, the first given before reperfusion. The group that did not receive alemtuzumab received basiliximab (2 doses of 20 mg on operative day and day 4), daclizumab (1 mg/kg on day 0 and 1 dose every other week for a total of 5 doses), OKT3, or ATG/thymoglobulin. Thymoglobulin (Sang Stat, Fremont, CA) was administered at a dose of 1.5 mg/kg daily starting on day 0 (day of transplant) and continued until calcineurin inhibitor levels were therapeutic or a maximum

Table 1
Definition of infectious complications

Infection	Definition
BK virus	Presence of BK viral load in blood or urine
CMV viremia	Positive quantitative serum polymerase chain reaction
CMV disease	Clinical signs and symptoms and histopathologic evidence of CMV (tissue invasive disease) or viral syndrome
Severe CMV disease	Tissue invasive disease requiring inpatient or intensive care
Recurrent CMV disease	Positive serum quantitative polymerase chain reaction and tissue invasive disease after a negative serum polymerase chain reaction test and resolution of clinical signs and symptoms of CMV after treatment of prior episode
Fungal infection (mold)	Histopathologic or cytopathologic examination showing hyphae from needle aspiration or biopsy specimen with evidence of associated tissue damage (either microscopically or unequivocally by imaging), or positive culture result for a sample obtained by sterile procedure from normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine and mucous membranes
Fungal infections (yeast)	Histopathologic or cytopathologic examination showing yeast cells (*Candida* spp. may also show pseudohyphae or true hyphae) from specimens of needle aspiration or biopsy excluding mucous membranes, or positive culture result on sample obtained by sterile procedure from normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine, sinuses, and mucous membranes, or microscopy (India ink, mucicarmine stain) or antigen positivity for *Cryptococcus* spp. in cerebrospinal fluid
Disseminated fungal infection	Evidence of invasive disease from >2 organ systems or bloodstream infection
Fungemia	Blood culture that yields fungi or yeast
Pneumonia	Respiratory symptoms and new infiltrate on chest radiograph
Bacteremia	Positive peripheral blood culture with a pathogenic organism. More than 2 positive blood cultures if organism was a common contaminant such as coagulase-negative *Staphylococcus*
Bacteriuria	>1000 CFU/mL
Rejection	Based on histopathology or attending physician notes if biopsy was contraindicated
Leukopenia	$<3.0 \times 10^3/\mu L$
Disseminated varicella disease	Multiple dermatomal involvement with clinical and/or microbiologic evidence of varicella

Adapted from Ascioglu et al. (2002). Both proven and probable fungal infections were included.