ELSEVIER

Experience With Alemtuzumab (Campath-1H) as Induction Agent in Renal Transplantation Followed by Steroid-Free Immunosuppression

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ABSTRACT

Background. The purpose of this study was to describe the initial experience with alemtuzumab as induction followed by steroid-free immunosuppression in kidney transplantation.

Methods. One hundred patients who received renal transplants from living and deceased donors were followed for a median period of 12 months (range = 1 to 12). A 30-mg intravenous dose of Alemtuzumab was administered on the transplant day, preceded by a 500-mg methylprednisolone dose. Maintenance immunosuppression consisted in the use of a calcineurin inhibitor in association with mycophenolic acid. Maintenance C2 levels of cyclosporine were between 400 and 600 ng/dL; or of tacrolimus, between 4 and 7 ng/dL. Prophylaxis included valgancyclovir, trimethoprim-sulfamethoxasole, and nystatin. All patients were evaluated for acute rejection episodes, adverse events, or death.

Results. The cumulative incidences of acute rejection at 1, 3, 6, and 12 months were 0%, 4% ($n = 4$), 5% ($n = 5$), and 8% ($n = 8$), respectively. Most episodes were Banff 1 a or b (88%). The infectious complication rate was 23%. There was no case of cytomegalovirus infection or posttransplant lymphoproliferative disease. Three patients died: one due to tuberculosis; one, sepsis; and one, an acute coronary event. No patient was lost to follow-up.

Conclusions. This study suggested the safety and efficacy of Campath-1H as an induction agent in renal transplant recipients.

CAMPATH-1H is a humanized monoclonal antibody directed against CD52 glycoprotein expressed on approximately 95% of peripheral blood lymphocytes, natural killer cells, monocytes, macrophages, and thymocytes; namely, almost all mononuclear cells.[1,2] CD52 is not present in granulocytes, platelets, erythrocytes, or hematopoietic stem cells. Its mechanism of Campath-1H action includes complement-mediated cytolysis, antibody-mediated cytotoxicity, and apoptosis.[3] It lyses lymphocytes via activation of in vitro complement and via antibody-dependent cellular cytotoxicity. Although Alemtuzumab is only approved by the Food and Drug Administration for the treatment of B-cell chronic lymphocytic leukemia, it has other uses in autoimmune diseases, such as rheumatoid arthritis, scleroderma, and multiple sclerosis. It was initially introduced into hematology by Hale and Waldmann,[1] and into renal transplantation by Calne et al.[4,5] Currently, low rates of renal transplant acute rejection have been achieved, thus improving graft survival after 1 year. Herein, we have described an early experience in terms of efficacy and induction safety of Campath-1H and steroid-free maintenance therapy in renal transplant recipients from living and cadaveric donors.

MATERIALS AND METHODS

Between November 2005 and November 2006, 129/35 living plus cadaveric donor renal transplantations were induced with alemtuzumab (Campath-1H). One-year follow-up was performed on 100 patients. All patients received 30 mg of Campath-1H as a single dose given intraoperatively after 1 g of acetaminophen, 2 mg of Clemastine, and 500 mg of methylprednisolone. Posttransplant immunosuppression was based on a calcineurin inhibitor (cyclosporine or tacrolimus) plus an antimetabolite (mycophenolate

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mofetil [MMF] or sodium mycophenolate) and 250 mg of methylprednisolone on day 1 and 125 mg on day 2. Oral prednisolone was not used. Immunosuppression was performed by adjusting the cyclosporine C2 levels between 400 and 600 ng/mL; C0 tacrolimus, between 4 and 7 ng/mL. The doses were 1500 mg MMF or 1080 mg EC- MPS. All patients received prophylaxis with a single intraoperative dose of a first- or second-generation cephalosporin; valgancyclovir doses adjusted to renal function for 12 weeks, trimethoprim-sulfamethoxazole, 480 mg/d for 24 weeks; and fungal prophylaxis with nystatin for 8 weeks.

No protocol biopsies were performed. Acute rejection, which was defined as a sudden increase of more than 25% in the baseline creatinine, was always confirmed by biopsy. Graft loss was defined as the patient's return to dialysis.

RESULTS

Among 100 de novo renal transplant recipients in the study, 88 grafts were from cadaveric donors and 12 from living donor. One subject underwent dual transplantation. The mean recipient age was 38.5 years (range, 15 to 69) with 6 patients younger than 18. There were 54 male and 46 female patients. Mortality was 3%: one sepsis due to pyelonephritis; one tuberculosis; and one acute coronary event.

Cumulative incidences of acute cellular rejection at 1, 3, 6, and 12 months were 0% ($n = 0$), 4% ($n = 4$), 5% ($n = 5$), and 8% ($n = 8$), respectively. There were 9 (53%) Banff 1 A, 6 (35.2%) Banff 1 B, and 1 (5.8%) Banff 2 A, and 1 (5.8%) humoral rejection according by Banff'97. Two of the rejections were corticoid resistant.

The infectious complication rate was 23% with a prevalence in the urinary tract, and no evidence of cytomegalovirus infection or posttransplant lymphoproliferative disease. There was no patient loss on follow-up.

DISCUSSION

In November 2005, we initiated a study of 100 de novo renal transplant recipients from living and cadaveric donors, using a single dose of Campath-1H. Our protocol differed from other reports which used more doses.[4,6,7] We employed maintenance therapy with reduced doses of cyclosporine or tacrolimus as well as a 75% dose of MMF sodium mycophenolate. In addition beyond day 1, the patients were steroid-free.

The group we followed showed a 17% incidence of acute cellular rejection episodes at 1 year, which was comparable to that reported by Ciancio et al,[4] namely, 16% ± 8%, and lower than the 24% of Leventhal's group.[8] Our rejection rate was low until the third month (4%), unlike protocols using other induction agents like basiliximab, where an 11.6% early rejection rate has been reported.[9–11] However, we observed an increased rejection rate after 6 months, which may reflect an inmunosuppressive deficiency, when lymphocyte repopulation forces adjustments in the maintenance therapy.[9] The severity of rejection in our study was mild: 15 patients were Banff grade 1 (a or b) (88%), comparable to reports by Kaufman et al (77%)[9] and by Ian et al (81%).[12] Only two cases were corticoid resistant.

The beneficial effects of steroid-free inmunosuppressive therapy are well known. Excellent results may be achieved in long-term therapies when patients receive adequate induction.[10,13,14] Another advantage of not using steroids is a reduced rate of adverse metabolic effects, such as osteoporosis, surgical wound infections, and posttransplant diabetes mellitus.[15] In addition there is a decreased risk of developing infections due to cytomegalovirus with this protocol,[16] as also seen among pancreas and liver transplantations.[17]

We decided to include six patients younger than 18 years in our follow-up; one of them showed humoral rejection followed by graft loss. While these are good results for this age group, a greater number of patients is necessary to compare our outcomes with the results described by Shapiro et al.[18,19]

In conclusion, alemtuzumab was a safe, effective induction agent for steroid-free maintenance immunosuppression in renal transplantation. It offered advantages of a single-dose application, good early acute rejection prophylaxis, and less need for calcineurin inhibitors.

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