The evolving role of alemtuzumab (Campath-1H) in renal transplantation

Phuong-Thu T Pham[1]
Gerald S Lipshutz[2]
Phuong-Truc T Pham[3]
Joseph Kawahji[1]
Jennifer S Singer[4]
Phuong-Chi T Pham[5]

[1]Division of Nephrology, Department of Medicine, Kidney and Pancreas Transplant Program, University of California at Los Angeles, David Geffen School of Medicine, Los Angeles, California; [2]Kidney and Pancreas Transplant Program, Department of Surgery and Urology, University of California at Los Angeles, David Geffen School of Medicine,Los Angeles, California; [3]Department of Science, Penn State University, Worthington-Scranton, Dunmore, Pennsylvania; [4]Renal Transplantation and Pediatric Urology, Department of Urology, University of California at Los Angeles, David Geffen School of Medicine, Los Angeles, California; [5]Division of Nephrology, Department of Medicine, University of California at Los Angeles, David Geffen School of Medicine, Los Angeles, and Olive-View-UCLA Medical Center, Sylmar, California, USA

Correspondence: Phuong-Thu Pham
Division of Nephrology, Department of Medicine, Kidney and Pancreas Transplantation, David Geffen School of Medicine at UCLA, 200 UCLA Medical Plaza, Suite 365C1, Los Angeles, CA 90095, USA
Tel +1 310 794 1757
Fax (310) 794-6553
Email ppham@mednet.ucla.edu

Abstract: The introduction of new immunosuppressive agents into clinical transplantation in the 1990s has resulted in excellent short-term graft survival. Nonetheless, extended long-term graft outcomes have not been achieved due in part to the nephrotoxic effects of calcineurin inhibitors (CNIs) and the adverse effects of steroid on cardiovascular disease risk factors. Induction therapy with lymphocyte depleting antibodies has originally been introduced into renal transplantation to provide intense immunosuppression in the early post-transplant period to prevent allograft rejection. Over the past half decade, induction therapy with both non-lymphocyte depleting (basiliximab and daclizumab) and lymphocyte-depleting antibodies (antithymocyte antibodies, OKT3, alemtuzumab) has increasingly been utilized in steroid or CNI sparing protocols in the early postoperative period. Alemtuzumab is a humanized monoclonal antibody targeted against CD52 on the surface of circulatory mononuclear cells. The ability of alemtuzumab (Campath-1H) to provide rapid and profound depletion of lymphocytes from the peripheral blood has sparked interest in the use of this agent as induction therapy in steroid and/or CNI minimization or avoidance protocols. This article provides an overview of the literarure on the evolving role of alemtuzumab in renal transplantation.

Keywords: alemtuzumab, Campath-1H, induction, renal transplantation, calcineurin inhibitor minimization, steroid avoidance

Introduction

Aggressive T-cell depletion in the peritransplant period has been suggested to prevent immune engagement during a period where there is a maximal drive towards lymphocyte activation, proliferation, and ultimately rejection.[1] Experimental studies have shown that perioperative lymphocyte depletion using pan-T-cell immunotoxins or other depleting antibodies induces tolerance in some rodents, canine, and nonhuman primate models.[2–3] Although immune tolerance has not been successfully achieved in clinical transplantation, lymphocyte depleting agents such as antithymocyte antibodies, or more recently alemtuzumab has increasingly been used as induction therapy in solid organ transplantation to induce a state of near-tolerance or "prope tolerance" whereby allografts can be maintained with reduced immunosuppression.

Alemtuzumab (Campath-1H) is a humanized immunoglobulin IgG1 monoclonal antibody directed against CD52, a cell surface glycoprotein expressed on circulating T-and B-cells and to a lesser extent on natural killer cells, monocytes, and macrophages. It has been suggested that after binding to its target, alemtuzumab causes cell death through complement-mediated cell lysis and antibody-mediated cellular cytotoxicity.[4–5] In vitro studies suggested that alemtuzumab may also enhance lymphocyte apoptosis through both caspase-dependent and caspase-independent pathways.[6] Alemtuzumab was approved by the US Food and Drug administration for the treatment of lymphoid malignancies in 1999. It has been used off-label in bone marrow transplantation to prevent graft versus host disease and to treat various autoimmune diseases such as

rheumatoid arthritis, scleroderma, and multiple sclerosis. Because of its rapid and profound lymphocyte depleting effects, alemtuzumab has increasingly been used off-label as induction therapy in renal transplantation as a means to allow safe avoidance or minimization of steroid or CNI therapy. Clinical studies evaluating the safety and efficacy of antibody pre-conditioning with alemtuzumab in conjunction with reduction in maintenance immunosuppression have yielded variable and conflicting results. In the current article we provide an overview of the literature and present our opinion on the evolving role of alemtuzumab in renal transplantation.

Early experiences

Alemtuzumab induction therapy in steroid avoidance and calcineurin inhibitor minimization protocols

Alemtuzumab was first introduced in renal transplantation in 1998 by Calne and colleagues.[7] In a small nonrandomized pilot study consisting of 13 primary deceased donor renal transplants, the authors demonstrated that the use of alemtuzumab as induction therapy (total 2 doses of 20 mg) followed by half-dose cyclosporine monotherapy resulted in satisfactory short-term outcomes. Patient and graft survival were 100% at 6-to 11-month follow-up. One patient developed steroid responsive biopsy-proven acute rejection. A second patient with impaired graft function showed no evidence of acute rejection on biopsy. No serious adverse events occurred during the study period.

The same group of investigators reported the long-term efficacy and safety of alemtuzumab induction therapy in deceased donor renal transplantation. In the extension of a single-center study consisting of 33 renal allograft recipients, Watson and colleagues[8] demonstrated that the use of alemtuzumab as induction therapy (20 mg given intravenously on day 0 and day 1 after transplant) followed by half-dose cyclosporine monotherapy resulted in satisfactory 5-year patient and graft survival comparable to that seen with standard triple immunosuppression consisting of cyclosporine (CSA), azathioprine, and prednisolone while avoiding steroid therapy. Although the incidence of acute rejection was similar between the two treatment groups at 5 years (alemtuzumab vs conventional triple therapy: 31.5% vs 33.6%, respectively), the pattern of rejection was different with 14% patients in the alemtuzumab group experiencing rejection over 1year post- transplant compared to none in the control group. Graft and patient survival and serum creatinine at 5-year follow up were similar in both groups despite the use of lower CSA concentration in the alemtuzumab group. The incidence of infections, de novo malignancies and serious adverse events were also comparable between the two treatment groups.

Alemtuzumab induction therapy without maintenance immunosuppression

Kirk and colleagues[9] hypothesized that aggressive pretransplant treatment with alemtuzumab would deplete peripheral and secondary lymphoid T cells and establish favorable conditions for the development of tolerance. In a pilot study consisting of 7 non-sensitized recipients of living donor kidneys, 3 to 4 doses of alemtuzumab (at 0.3 mg/kg per dose) were administered intravenously in the peri-transplant period without additional maintenance immunosuppression. Despite profound lymphocyte depletion in the periphery and secondary lymphoid tissues, all patients developed acute rejection within the first month that were characterized predominantly by monocytic (not lymphocytic) infiltrates with only rare T cells in the periphery blood or allograft. Most episodes were reversed with steroid (n = 5). One patient required OKT3 and one responded to sirolimus alone. Sirolimus maintenance therapy was initiated in all patients. There were no episodes of late acute rejection at 12 month follow-up. This study demonstrated that alemtuzumab alone does not induce tolerance in clinical transplantation. A prominent role for early responding monocytes in human allograft rejection has been suggested.

Alemtuzumab induction and short-term deoxypergualin monotherapy

The failure of alemtuzumab induction alone to induce tolerance in humans and the observation that lymphopenic rejections were characterized predominantly by graft infiltration with monocytes and macrophages have led Kirk and colleagues[10] to hypothesize that monocytes were under-immunosuppressed by T-cell depletion alone and hence available as alternative effector cells for T-cell depletion-resistant rejection. The same group of investigators conducted a trial to determine whether T-cell depletion with alemtuzumab in combination with a brief course of deoxyspergualin (DSG), a drug with inhibitory effect on monocytes and macrophages would induce tolerance in recipients of renal allograft transplants. Five recipients of primary live donor kidneys were treated peri-operatively with 4 doses of alemtuzumab at 0.3 mg/kg/dose. All patients also received DSG at a total dose of 36.5 mg/kg.

Despite profound T-cell depletion and therapeutic DSG dosing, all patients developed reversible rejection that was similar in timing, histology, and transcriptional profile to that seen in patients treated with alemtuzumab alone. It was thus speculated that several chemokines continue to be transcribed post-transplantation despite the absence of infiltrating lymphocytes or monocytes. These chemokines, in turn can serve to gradually accumulate sufficient residual monocytic antigen presenting cells and allospecific lymphocytes to eventually mount an immune response.

Early experiences: summary

Early studies have shown that antibody preconditioning with alemtuzumab without maintenance immunosuppression failed to achieve tolerance in clinical transplantation whereas acceptable short-term patient and graft outcomes could be achieved with alemtuzumab induction and minimization of immunosuppression (steroid-free CNI-minimization protocols).

Alemtuzumab induction and CNI avoidance protocols

Sirolimus monotherapy

In a pilot trial conducted by Knechtle and colleagues[11] 29 recipients of primary renal allograft transplants were given 2 doses of alemtuzumab (20 mg/dose) on day 0 and 1 (first 24 patients), and on day –1 and 0 (patients 25–29). In the first 24 living donor recipients, sirolimus monotherapy was started the day after transplant. Six patients (25%) experienced severe acute rejection resulting in one graft loss. Most acute rejection episodes occurred within the first 3 weeks post-transplant and were predominantly humoral (4/6) rather than cellular in nature. Due to the unexpected high incidence of early acute humoral rejection (AHR) in the first 24 patients, the subsequent 5 patients were treated with a modified protocol that included alemtuzumab on day –1 and 0, thymoglobulin on day 1, and steroid tapering over a 14 day period. A single dose of thymoglobulin was used to target CD52 negative cells which are usually present in 1% to 3% of a normal subject's T cells. In addition, recovery T-cells after alemtuzumab induction were found to be largely CD52 negative. Despite the theoretical advantage of thymoglobulin, 2 of 5 patients experienced reversible rejection episodes within the first month posttransplant (one with a humoral component). Seven of 29 patients with rejection were switched to standard triple therapy with tacrolimus, mycophenolate mofetil (MMF), and prednisone.

At 3-year follow-up,[12] 13 patients (46%) had experienced acute rejection episodes. Of these, 7 (54%) had a humoral component. Graft and patient survival were 96% and 100%, respectively. Eighteen patients (67%) were on a steroid-free regimen, and 15 of 27 patients with a functioning graft were on monotherapy (13 on sirolimus, 1 tacrolimus, and 1 on prednisone). No serious infections occurred.

Sirolimus and mycophenolate mofetil combination therapy

In view of high acute rejection rates that occurred with alemtuzumab induction and sirolimus monotherapy, Flechner and colleagues[13] performed a pilot study in which alemtuzumab induction was followed by sirolimus and MMF maintenance therapy in a CNI-free and steroid-free immunosuppressive regimen. Twenty two primary renal allograft recipients were given alemtuzumab induction (30 mg on day 0 and 1), sirolimus and MMF maintenance therapy. With a mean follow-up of 15.9 months, patient and graft survival were 96% and 87%, respectively. Of the 19 surviving grafts, 18 (95%) remained steroid free and 15 (79%) were CNI-free. However, acute rejections occurred in 8 (36.8%). Of these, 2 were humoral rejections. Although the overall infection rates were low, 2 patients developed severe acute respiratory distress syndrome at month 3 and 7, resulting in mortality in 1 and graft loss in the other. No cancer or PTLD was observed. Leukopenia was common, requiring MMF dose reduction in 6/22 (27%) patients. Although the results of this study suggested that the goal of the study was achieved, ie, the majority of patients were CNI- and steroid-free at 1 year, there was a concern over a higher than expected rate of acute rejection, leukopenia, and possible pulmonary toxicity.

Alemtuzumab, MMF, steroids and CNI avoidance vs alemtuzumab, CNI, MMF and steroids

Retrospective analysis of the OPTN/UNOS database[14] revealed that alemtuzumab induction (n = 690) was associated with a lower rate of acute rejection during the first six months post-transplant compared with no induction (n = 4,364), ATG (n = 4,930), and Il-2R antibody induction (n = 4,378) (2.3% vs 7.6% vs 3.4% vs 4.8%, respectively, $p < 0.001$). However, there was an increased incidence of acute rejection at 6 months and 1 year with alemtuzumab (14.5% and 19.2%) compared to no induction (12.7% and 14.8%, $p < 0.001$), ATG (8.2% and 10.2%, $p < 0.001$), and Il-2R antibody

(11.1% and 13.0%, $p < 0.001$) with no difference in adjusted relative risk for graft loss. Further analysis demonstrated that alemtuzumab recipients receiving FK or CSA, MMF, and steroids had increased graft (FK/MMF/steroids, $p < 0.001$), CSA/MMF/steroids, $p = 0.007$) and rejection-free survival (FK/MMF/steroids, $p = 0.006$) over 24 months compared with no CNI, MMF, and steroids. It should be noted that data on dosing information were not provided, hence it is unknown if patients receiving alemtuzumab induction were maintained on reduced dose CNI compared to those receiving ATG or IL-2R antibody induction.

Low-dose sirolimus vs low-dose CSA in combination therapy with low-dose MMF

In a prospective, single-center randomized study to determine the influence of immunosuppressive agents on regulatory T cells (Treg) homeostasis in renal transplant recipients who underwent profound T cell depletion with alemtuzumab and maintenance therapy with low-dose sirolimus (n = 11) vs low-dose CSA (n = 10) in combination therapy with low-dose MMF, Noris and colleagues[15] demonstrated stable graft function in both groups at 6, 12, and 24 months. However, in sirolimus-treated patients, glomerular filtration rate (GFR) was numerically higher than in the CSA group at all time points. One patient on sirolimus and two on CSA had an episode of steroid responsive acute rejection at 14, and 9 and 210 days after transplantation, respectively. The investigators further demonstrated that during immune reconstitution, $CD4^+CD25^{high}$ cells that expressed FOXP3 underwent homeostatic peripheral expansion that was more intense in patients who received sirolimus than in those who were given CSA. On the basis of these data, it is hypothesized that lymphopenia and calcineurin-dependent signaling could be instrumental to achieving pro-tolerogenic Treg expansion in the clinical transplant setting.

To test the hypothesis that the expansion of circulating $CD4^+CD15^{high}$ regulatory T cells might translate into more effective protection against chronic allograft injury, the same group of investigators[16] compared the long-term clinical outcomes and biopsy findings of sirolimus- (n = 11) vs CSA-treated patients (n = 10). Despite 4-fold higher $CD4^+CD25^{high}$ Treg counts, sirolimus-treated patients – compared to CSA-treated patients, had a significantly higher tubular C4d staining score (sirolimus vs CSA: 1.1 ± 0.6 vs 0.2 ± 0.3, $p < 0.01$) with nonsignificant trends to higher chronic allograft damage index score, faster GFR and RPF decline, and more clinical proteinuria. Furthermore, there was no significant correlation between Treg counts and any considered outcome variable in the study group as a whole and within each cohort. Hence, these data suggest that despite enhanced Treg expression, low-dose sirolimus combined to alemtuzumab induction and MMF-based-steroid-free maintenance therapy does not appreciably protect renal transplant recipients from chronic allograft injury and dysfunction.

Alemtuzumab induction and CNI avoidance: summary

Alemtuzumab induction and CNI avoidance appear to be relatively ineffective in the prevention of acute rejection episodes and to lack protection against antibody-mediated rejection. Despite the enhanced expression of regulatory T cells and its strong antiproliferative effect on alloreactive T cells, sirolimus-based immunosuppression in CNI avoidance protocols fails to protect renal allograft from chronic injury and dysfunction.

Alemtuzumab and minimization of immunosuppression (CNI-based immunosuppressive protocols with or without steroids)

Alemtuzumab induction and reduced dose steroids

In a single-center retrospective study, Knechtle and colleagues[17] reported their experiences with 126 consecutive renal allograft recipients who received two doses of alemtuzumab on days 0 and 1, in combination therapy with very low dose steroids (10 mg methylprednisolone a day), MMF, and either tacrolimus or CSA; the outcomes were compared with 1115 renal allograft recipients treated at the same institution who received either an anti-CD25 antibody (n = 799), thymoglobulin (n = 160) or other antibody induction therapy (n = 156) in combination with MMF, CNI (tacrolimus or CSA), and higher dose steroid (steroid taper to 10 mg by 3 months). Follow-up was 12 months for the alemtuzumab group and 48 to 72 months for the other 3 groups. The overall incidence of rejection was lower in the alemtuzumab compared to the control groups ($p = 0.037$). At 200 days follow-up, alemtuzumab-treated patients had significantly less rejection compared to control groups ($p = 0.0096$). Furthermore, patients with delayed graft function had significantly improved graft survival compared to the other cohorts ($p = 0.0119$). No difference in infections or malignancies among the four groups was seen at latest

follow-up. Subsequent analysis at 3-year follow-up revealed more viral and fungal infections in the thymoglobulin and alemtuzumab group. There was no difference in rejection rate. However, graft survival was better in the anti-CD25 receptor antibody induction group than in the other two groups.

Alemtuzumab induction and CNI monotherapy (steroid avoidance)

In a prospective randomized three-arm trial in which induction therapy with thymoglobulin, alemtuzumab (0.3 mg/kg given intravenously on day 0 and day 4), and daclizumab were compared, Cianco and colleagues[18] have shown comparable patient and graft survival, acute rejection rates, and renal function among the three treatment groups at a median follow-up of 15 months. All patients received tacrolimus, MMF, and steroids. However, the alemtuzumab group received half the dose of tacrolimus and no steroids after the first week. In addition, 80% of the patients remained steroid-free 1 year after transplant.

In a prospective multicenter randomized controlled trial comparing alemtuzumab induction (two 20 mg doses given intravenously) and low-dose CSA monotherapy (n = 20) with conventional triple therapy with CSA, azathioprine, and steroids (n = 10), Vathsala and colleagues[19] demonstrated comparable acute rejection rates, graft and patient survival, and renal function between the two treatment groups at 6 months follow-up. Fifteen of the 20 patients (88%) with functioning grafts in the alemtuzumab group were steroid free. Thrombocytopenia and the overall incidence and spectrum of infections were comparable between the two groups.

Alemtuzumab and space-weaning tacrolimus monotherapy

Tan and colleagues[20] compared the outcomes of 205 living donor renal transplant recipients who received alemtuzumab induction (30 mg given intravenously on day 0) and spaced-dose tacrolimus monotherapy with 47 historical controls who were transplanted prior to the induction era, and who were treated with conventional standard triple therapy with tacrolimus, MMF, and prednisone. At a mean follow-up of 493 days, 7.3% in the alemtuzumab group were on twice a day dosing, more than one third (36.6%) were on once daily, 22% were on every other day, 17% were on 3 times a week, 2% were on twice per week, and 1% were on once per week. Approximately 10% were on multiple immunosuppressive drugs. Actuarial 1-year patient and graft survival were 98.6% and 98.1% in the alemtuzumab group, compared to 93.6% and 91.5% in the control group, respectively. The incidence of acute cellular rejection (ACR) at 1 year was 6.8% in the alemtuzumab group and 17.0% in the historic control group ($p < 0.05$). There was no cytomegalovirus disease or infection. The authors concluded that this study confirms the short-term safety and efficacy of alemtuzumab induction and tacrolimus monotherapy in living donor renal transplant.

Shapiro and colleagues[21] compared thymoglobulin (n = 101) or alemtuzumab 30 mg (n = 90) induction and minimization of immunosuppression with conventional triple immunosuppression with tacrolimus, prednisolone, and either MMF or sirolimus (n = 152). In both induction groups spaced-weaning tacrolimus monotherapy was attempted 3 to 4 months posttransplant. There was no significant difference in overall patient and graft survival between both lymphoid depleting and historical control groups at 12- to 18-month follow-up. However, survival of live donor grafts was better in the thymoglobulin and alemtuzumab induction groups than in live donor historical controls. There was a significant difference in the incidence and time to acute rejection among the three treatment groups. In the thymoglobulin-treated patients, the onset of rejection was earlier ($p < 0.001$) and the incidence was higher than in either the alemtuzumab or historical control patients. Of note, because rejection episodes were associated with too rapid weaning in the thymoglobulin series, spaced dosing beyond every other day or three times a week was not attempted in the alemtuzumab group until at least 1 year unless there were specific indications (eg, drug nephrotoxicity or neurotoxicity). The incidence of rejection during the first 6 months in alemtuzumab-treated patients was 1%. Rejections that occurred after 6 months were frequently associated in both the thymoglobulin- and alemtuzumab-treated patients with attempts to space wean. At 24- to 39-month follow-up, 68% of patients (56/83) with functioning grafts in the thymoglobulin-treated group were on space doses of maintenance immunosuppression, 25% were on monotherapy and 7% were on more than one immunosuppressant. In the alemtuzumab-treated group, 74% (62/84) were on space weaning, 14% were on daily monotherapy, and 12% received more than a single agent at 12-18 month follow-up. The authors concluded that after lymphoid depletion, kidney transplantation can be readily accomplished under minimal immunosuppression with less dependence on late immunosuppression and a better quality of life. Alemtuzumab has been suggested to be the more effective agent.

Alemtuzumab induction and minimization of immunosuppression (CNI-based immunosuppressive protocols with or without steroids): summary

In low immunological risk renal transplant recipients, excellent short- and intermediate-term outcomes can be achieved with alemtuzumab induction and CNI minimization with or without steroids. Although alemtuzumab induction may allow space-weaning tacrolimus monotherapy, it should be noted that the study by Tan and colleagues and that of Shapiro and colleagues are limited by their retrospective nature and long-term followup is lacking. In addition, in Shapiro's study, acute rejection episodes that occurred after 6 months were frequently associated with attempts to space wean.

Alemtuzumab induction in high risk renal transplant candidates

High risk renal transplant candidates have variously been defined as those with high immunological risk (such as highly sensitized or retransplant candidates, African Americans or Hispanics), or those at high-risk for delayed graft function (such as recipients of organs from expanded criteria donors or from donors after cardiac death, prolonged cold ischemia time, donor elevated creatinine or donor acute tubular necrosis).

The use of alemtuzumab induction in high-risk renal transplant candidates has not been consistently shown to offer any advantage over traditional induction agents. In the following section, selected studies utilizing alemtuzumab induction in the so called "high risk" population are presented.

African Americans and hispanic ethnicity

In a single-center, prospective, randomized trial consisting of predominantly African Americans and Hispanics, Cianco and colleagues[22] have shown that alemtuzumab induction and minimization of immunosuppression were less effective than either thymoglobulin or daclizumab and higher maintenance immunosuppression. During the study period, 90 recipients of deceased donor renal transplants were randomized to receive either thymoglobulin during the first week post-transplant (Group A), alemtuzumab on post-operative day 0 and 4 (Group B), or daclizumab at 1 mg/kg on the day of surgery and every 2 weeks × 4 (Group C). African Americans and Hispanics comprised more than 50% in each group. All patients received tacrolimus, MMF and steroid immunosuppression. However, patients in group B received half-dose MMF and steroid was withdrawn after the first week post-transplant. At a minimum follow-up of 27 months, there were no overall group differences in patient or graft survival, but a trend towards worse death-censored graft survival in group B ($p = 0.05$). Acute rejection rates were not significantly different among the treatment groups. The incidence of chronic allograft nephropathy was higher in group B than A and C ($p = 0.008$). Mean calculated creatinine clearances at 24 months were 81.1 ± 5.5, 64.4 ± 4.5, and 80.7 ± 5.7 mL/min, for groups A, B, and C, respectively ($p = 0.01$ for B vs average A and C).

In a single center retrospective study consisting of the first 75 primary renal transplant patients given alemtuzumab induction and minimization of immunosuppression (low-dose tacrolimus, reduced dose MMF and steroid withdrawal after the first week posttransplant), Cianco and colleagues[23] demonstrated that while three-year actuarial patient and graft survival rates were comparable between African Americans ($n = 20$), Hispanics ($n = 32$), and non-African Americans non-Hispanic ($n = 23$) ($p = NS$), higher incidences of biopsy-proven acute rejection, chronic allograft dysfunction, and borderline worse renal function were seen among African Americans in comparison with the other patient subgroups.

In a single-center, nonrandomized, retrospective, sequential study design to evaluate outcomes in kidney transplant recipients receiving either a single dose (30 mg) of alemtuzumab ($n = 123$) or basiliximab ($n = 155$) induction in combination therapy with tacrolimus, MMF and steroid avoidance, Kaufman and colleagues[24] reported a lower rate of early rejection (<3 months) in the alemtuzumab (4.1%) vs the basiliximab (11.6%) group. However, at 1-year follow-up, the rejection rates were comparable between the two treatment groups. Further analysis revealed that patient and graft survival and rejection rates were nearly identical between caucasians ($n = 76$) and African Americans ($n = 28$) receiving alemtuzumab (96.1% vs 96.4%, respectively). Although maintenance immunosuppressive regimens were identical in the two induction groups, alemtuzumab-treated patients received significantly less MMF at all time points analyzed over a 3-year period, as well as significantly less tacrolimus at all time points analyzed over a 2-year period.

Alemtuzumab induction in kidney transplantation from donors after cardiac death (DCD)

In a retrospective study comparing the outcomes of induction therapy with either alemtuzumab, interleukin-2 receptor (IL-2R) antagonists or anti-thymocyte globulin (ATG) in

renal transplantation from donors after cardiac death, Schadde and colleagues[25] found that induction with alemtuzumab does not confer any advantage over traditional induction agents. All patients received triple immunosuppression with CNI, MMF, and steroids. Patients were stratified into high-risk and low-risk groups. The latter was defined as those with panel reactive antibody >20%, retransplants, and African American ethnicity. Comparing alemtuzumab to either IL-2R antagonist or ATG, the time to acute rejection was not significantly different among the three induction regimen in both high- and low-risk groups. While there was no statistically significant difference in graft survival over 3 years, there was a trend for worse patient survival in high-risk recipients receiving alemtuzumab induction ($p = 0.055$). It should be noted that the high-risk group consisted of a small sample size (Low-risk group: IL-2R, n = 43; alemtuzumab, n = 61. High-risk group: ATG, n = 21; alemtuzumab, n = 20). The antibody induction strategies did not lead to significantly different outcomes in patients receiving kidneys from donation after cardiac death.

Alemtuzumab induction in high-risk renal transplant recipients (The University of California at Los Angeles experience)

This is a retrospective review of a single-center prospectively maintained database of high-risk renal transplant patients who received lymphocyte-depleting antibody induction. Patients received thymoglobulin induction (n = 54) in 2004, and alemtuzumab induction (n = 46) in 2005. "High-risk" was defined as highly sensitized patients or recipients with anticipated delayed graft function such as long cold ischemia time (CIT), expanded criteria donor (ECD) kidney, donor after cardiac death (DCD), and/or elevated donor terminal creatinine). All patients were maintained on non-minimization triple therapy consisting of a calcineurin inhibitor, MMF, and prednisone. There were no statistical differences in the groups with regards to recipient gender, ethnicity, living or deceased donor, cold ischemia time, or number of HLA matches. One-year patient and graft survival rates were comparable between the two treatment groups (Thymoglobulin vs alemtuzumab: 96.2% vs 95.1%, and 90.5% vs 90.7%, respectively). There was no statistically significant difference in rejection (alemtuzumab vs thymoglobulin: 10.9% vs 16.7%) but humoral rejection was more common in the thymoglobulin group. The incidences of DGF, viral, and fungal infections were also similar between the two treatment groups. Our data support the use of either thymoglobulin or alemtuzumab induction in high-risk renal transplant recipients. Large randomized, controlled trials with long-term follow-up are needed.

Alemtuzumab in high risk renal transplant candidates: summary

While alemtuzumab induction and minimization of immunosuppression appear to provide effective immunosuppression in high-risk renal transplant recipients, an increased rate of acute rejection and chronic allograft nephropathy have variably been reported. Whether the latter was due to the difference in the levels of maintenance immunosuppression is speculative. Early studies from our own center suggest that alemtuzumab induction and non-minimization of immunosuppression is effective in high-risk renal transplant recipients. Long-term follow-up is needed.

Discussion

In summary, early experiences have demonstrated that alemtuzumab induction alone does not induce tolerance in clinical transplantation while alemtuzumab and sirolimus-based immunosuppression in CNI-avoidance protocols resulted in unacceptable high acute cellular and/or humoral rejection rates. In contrast, excellent short- and intermediate- term outcomes can be achieved in low-immunological risk renal transplant recipients receiving alemtuzumab induction in conjunction with reduction in immunosuppression in CNI-based steroid avoidance protocols.

Pearl and colleagues[26] first studied the phenotype and characteristics of post-depletional T cells in renal transplant recipients undergoing profound T-cell depletion with alemtuzumab or rabbit anti-thymocyte globulin. The authors demonstrated that peripheral T cells from transplant recipients undergoing aggressive T-cell depletion consist almost exclusively of depletion-resistant effector memory T cells (CD3+CD4+CD45RA-CD62L-CCR7 phenotype) that expand in the first month and are uniquely prevalent at the time of rejection. Furthermore, in vitro studies revealed that these cells were resistant to steroids, deoxypergualin and sirolimus, but were effectively inhibited by low-dose calcineurin inhibitors. Memory cells have been shown to be exquisitely sensitive to low concentrations of tacrolimus both in terms of proliferation and cytokine production. It is conceivable that the selective resistance of effective memory T cells to immunosuppressants accounts for the higher incidence of acute rejection observed in renal transplant recipients receiving alemtuzumab preconditioning and sirolimus-based immunosuppression compared to those maintained on CNI-based immunosuppression.

It has been suggested that the high incidence of humoral rejection associated with alemtuzumab induction is due to its predominant effect on profound depletion of circulating lymphocytes but not circulating monocytes. In a study to investigate the role of monocytes in humoral rejection and the rates of C4d positivity in unremarkable protocol biopsies vs biopsies with acute tubular necrosis (ATN) vs biopsies with acute cellular rejection in renal transplant recipients receiving alemtuzumab induction Zhang and colleagues[27] demonstrated a low rate of C4d positive staining in both the protocol and ATN group. In contrast, a 47% rate of C4d positivity was noted in the acute cellular rejection (ACR) group. Furthermore, in ACR cases, CD68 positive monocytes were composed of nearly 60% inflammatory cells compared with 39% CD3 positive lymphocytes. Double staining revealed co-localization of positive C4d staining in endothelium and marginating CD68 positive monocytes. The high percentage of monocytes observed in ACR cases led the authors to speculate that monocytes are less sensitive to alemtuzumab depletion and are involved in antibody-mediated rejection.

Role of alemtuzumb in renal transplantation: the authors' opinion

The role of alemtuzumab in renal transplantation is currently not well defined due to the lack of large, prospective, controlled trials and the mixed results obtained from single-center experiences. The latter may be due in part to different study designs, alemtuzumab dosing regimen, and heterogeneous maintenance immunosuppressive therapy. Nonetheless, based on currently existing literature, the use of alemtuzumab induction and minimization of immunosuppression in a regimen consisting of CNI-based immunosuppression with or without steroids provides effective immunosuppression in low immunological risk renal transplant recipients (eg, living or deceased primary transplants, non-sensitized recipients, non-African Americans). In high-risk renal transplant candidates, antibody preconditioning with alemtuzumab does not appear to offer any advantage over traditional induction agents. Whether the use of alemtuzumab induction facilitates minimization of immunosuppression in high-risk candidates needs further studies. Nonetheless, monitoring patients for the development of donor specific antibody (DSA) may be invaluable in the detection of imminent rejection and the information obtained may assist clinicians in redirecting therapy. In a retrospective study consisting of a heterogenous group of transplant recipients (low- and high-risk recipients) receiving alemtuzumab preconditioning with tacrolimus monotherapy, Shapiro and colleagues[28] have shown that intensification of immunosuppression upon detection of DSA in recipients who underwent tacrolimus weaning resulted in disappearance of DSA in 40% of patients and excellent graft survival at 1- and 2-year follow-up. Whether immune monitoring (such as measurement of serum granzyme B and perforin) may serve as a useful tool for the early detection of rejection and allow safer reduction in immunosuppression is a subject of ongoing research. Indeed, the dosing strategy for alemtuzumab and the optimal maintenance immunosuppressive regimen remain to be defined.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Elster EA, Hale DA, Mannon RB, et al. The road to tolerance: renal transplant tolerance induction in nonhuman primate studies and clinical trials. *Transplant Immunology*. 2004;13:87–99.
2. Knechtle SJ, Vargo D, Fechner J, et al. FN18-CRM9 immunotoxin promotes tolerance in primate renal allografts. *Transplantation*. 1997;63:1–6.
3. Thomas JM, Neville DM, Contreras JL, et al. Preclinical studies of allograft tolerance in rhesus monkeys: a novel anti-CD3-immunotoxin given peritransplant with donor bone marrow induces operational tolerance to kidney allografts. *Transplantation*. 1997;64:124–135.
4. Weaver TA, Kirk A. Alemtuzumab. *Transplantation*. 2007;84(12): 1545–1547.
5. Nuckel H, Frey UH, Roth A, et al. Alemtuzumab induces enhanced apoptosis in vitro in B-cells from patients with chronic lymphocytic leukemia by antibody-dependent cellular cytotoxicity. *Eur J Pharmacol*. 2005;514:217–224.
6. Stanglmaier M, Reis S, Hallek M. Rituximab and alemtuzumab induce a nonclassic, caspase-independent apoptotic pathway in B-lymphoid cell lines and in chronic lymphocytic leukemia cells. *Ann Hematol*. 2004;83:634–654.
7. Calne R, Friend P, Moffatt S, et al. Prope tolerance, perioperative Campath-1H, and low-dose cyclosporine monotherapy in renal allograft recipients. *Lancet*. 1998;351(9117):1701–1702.
8. Watson CJ, Bradley JA, Friend PJ, et al. Alemtuzumab (CAMPATH) induction therapy in cadaveric kidney transplantation-Efficacy and safety at five years. *Am J Transplant*. 2005;5:1347–1353.
9. Kirk AD, Hale DA, Mannon RB, et al. Results from a human renal allograft tolerance trial evaluating the humanized CD52-specific monoclonal antibody Campath-1H. *Transplantation*. 2003;76(1):120–129.
10. Kirk AD, Mannon RB, Kleiner DE, et al. Results from a human renal allograft tolerance trial evaluating T-cell depletion with alemtuzumab combined with deoxyspergualin. 2005;80(8):1051–109.
11. Knechtle SJ, Pirsch JD, Fechner Jr J, et al. Campath-1H induction plus rapamycin monotherapy for renal transplantation: Results of a pilot study. *Am J Transplant*. 2003;3:722–730.
12. Barth RN, Janus CA, Lillesand CA, et al. Outcomes at 3 years of a prospective pilot study of Campath-1H and sirolimus immunosuppression for renal transplantation. *Transplant Int*. 2006;19:885–892.
13. Flechner SM, Friend PJ, Brockmann J, et al. Alemtuzumab induction and sirolimus plus mycophenolate mofetil maintenance for CNI and steroid-free kidney transplant immunosuppression. *Am J Transpl*. 2005;5:3009–3014.
14. Huang E, Cho YW, Hayashi R, et al. Alemtuzumab induction in deceased donor kidney transplantation. *Clin Transplant*. 2007;84:821–828.

15. Noris M, Casiraghi F, Todeschini M, et al. Regulatory T cells and T cell depletion : Role of immunosuppressive drugs. *J Am Soc Nephrol*. 2007;18:1007–1018.
16. Ruggenenti P, Perico N, Gotti E, et al. Sirolimus versus cyclosporine therapy increases circulating regulatory T cells, but does not protect renal transplant patients given alemtuzumab induction from chronic allograft nephropathy. *Clin Transplant* 2007;84(8):956–964.
17. Knechtle SJ, Fernandez LA, Pirsch JD et al. Campath-1H in renal transplantation: The University of Wisconsin experience. *Surgery*. 2004;136(4):754–760.
18. Cianco G, Burke GW, Gaynor JJ, et al. A randomized trial of three renal transplant induction antibodies: early comparison of tacrolimus, mycophenolate mofetil, and steroid dosing, and newer immune-monitoring. *Transplantation*. 2005;80:457–465.
19. Vathsala A, Ona ET, Tan S, et al. Randomized trial of alemtuzumab for prevention of renal function after kidney transplantation. *Transplantation*. 2005;80:765–774.
20. Tan HP, Kaczorowski DJ, Basu A, et al. Living donor renal transplantation using alemtuzumab induction and tacrolimus monotherapy. *Am J Transplant*. 2006;6(10):2409–2417.
21. Shapiro R, Basu A, Tan H, et al. Kidney transplantation under minimal immunosuppression after pretransplant lymphoid depletion with Thymoglobulin or Campath. *J Am Coll Surg*. 2005;200:505–515.
22. Cianco G, Burke GW, Gaynor JJ, et al. A randomized trial of thymoglobulin vs alemtuzumab (with lower dose maintenance immunosuppression) vs daclizumab in renal transplantation at 24 months of follow-up. *Clin Transplant*. 2008;22:200–210.
23. Cianco G, Burke GW, Gaynor JJ, et al. Campath-1H induction therapy in African American and Hispanic first renal transplant recipients: 3-year acturial follow-up. *Transplantation*. 2008;85(4):507–516.
24. Kaufman DB, Leventhal JR, Axelrod D, et al. Alemtuzumab induction and prednisone-free maintenance immunotherapy in kidney transplantation: Comparison with basiliximab induction-Long term results. *Am J Transplant*. 2005;5:2539–2548.
25. Schadde E, D'Alessandro AM, Knechtle SJ, et al. Alemtuzumab induction and triple maintenance immunotherapy in kidney transplantation from donors after cardiac death. *Transplant Int*. 2008;21:625–636.
26. Pearl JP, Parris J, Hale DA, et al. Immunocompetent T-cells with a memory-like phenotype are the dominant cell type following antibody-mediated T-cell depletion. *Am J Transplant*. 2005;5:465–474.
27. Zhang PI, Malek SK, Blasick TM, et al. C4d positivity is often associated with acute cellular rejection in renal transplant biopsies following Campath-1H (Alemtuzumab) induction. *Ann Clin Lab Sci*. 2007;37:121–126.
28. Shapiro R, Zeevi A, Basu A, et al. Alemtuzumab preconditioning with tacrolimus monotherapy-The impact of serial monitoring for donor-specific antibody. *Transplantation*. 2008;85(8):1125–1132.