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Randomized trial of rATg/Daclizumab vs. rATg/Alemtuzumab as dual induction therapy in renal transplantation: Results at 8 years of follow-up

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ABSTRACT

Our goal in using dual induction therapy is to bring the kidney transplant recipient closer (through more effectively timed lymphodepletion) to an optimally immunosuppressed state. Here, we report long-term results of a prospective randomized trial comparing (Group I,$N = 100$) rATG/Dac (3 rATG, 2 Dac doses) vs. (Group II,$N = 100$) rATG/Alemtuzumab(C1H) (1 dose each), using reduced tacrolimus dosing, EC-MPS, and early corticosteroid withdrawal. Lower EC-MPS dosing was targeted in Group II to avoid severe leukopenia. Median follow-up was 96 mo post-transplant. There were no differences in 1st BPAR (including borderline) rates: 10/100 vs. 9/100 in Groups I and II during the first 12mo($P = 0.54$), and 20/100 vs. 20/100 throughout the study($P = 0.90$). Equally favorable renal function was maintained in both treatment arms(N.S.). While not significant, more patients in Group II experienced graft loss, 25/100 vs. 18/100 in Group I($P = 0.23$). Actuarial patient/graft survival at 96 mo was 92%/83% vs. 85%/73% in Groups I and II(N.S.). DWFG-due-to-infection(N.S.), EC-MPS withholding-due-to-leukopenia during the first 2mo($P = 0.03$), and incidence of viral infections($P = 0.09$) were higher in Group II, whereas EC-MPS withholding-due-to-GI symptoms was higher in Group I($P = 0.009$). No other adverse event differences were observed. While long-term *anti*-rejection and renal function efficacy were demonstrated in both treatment arms, slight over-immunosuppression of Group II patients occurred.

List of abbreviations

AR	acute rejection
BPAR	biopsy-proven acute rejection
C1H	Campath-1H (Alemtuzumab)
CAI	chronic allograft injury
CNI	calcineurin inhibitor
CMV	cytomegalovirus
Cr	creatinine
Dac	Daclizumab
DD	deceased donor
DGF	delayed graft function
DSA	donor specific antibody
EC-MPS	enteric-coated mycophenolate sodium
eGFR	estimated glomerular filtration rate
GI	gastrointestinal
IMPDH	inosine monophosphate dehydrogenase
LD	living donor
MMF	mycophenolate mofetil
mo	months
NODAT	new onset diabetes mellitus after transplant
N.S.	nonsignificant
rATG	rabbit antithymocyte globulin
S.E.	standard error
SGF	slow graft function
WBC	white blood cell count

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1. Introduction

During years 2000–2001 our standard immunosuppressive regimen consisted of single agent induction with the nondepleting human *anti*-interleukin-2 receptor (CD25) monoclonal antibody daclizumab(Dac), with maintenance therapy consisting of reduced tacrolimus dosing, mycophenolate mofetil(MMF), and corticosteroids; in fact, we achieved a one year biopsy-proven acute rejection(BPAR) incidence of only 2% with this regimen [1–4]. However, our subsequent randomized trial comparing the use of three single induction agents, the lymphodepleting polyclonal antibody rabbit antithymocyte globulin(rATG)(Thymoglobulin®) vs. the lymphodepleting humanized anti-CD52 monoclonal antibody alemtuzumab(Campath-1H®)(C1H) vs. Dac yielded disappointing results, with one year BPAR incidences of 12%–19% in the 3 treatment arms [5–8]. We then changed our standard immunosuppressive regimen to include early corticosteroid withdrawal (by 7–10 days post-transplant) along with continued use of reduced TAC dosing and an inosine monophosphate dehydrogenase(IMPDH) inhibitor. In an attempt to achieve a more favorable one year BPAR incidence, we also initiated dual induction therapy with rATG and Dac, using fewer doses of each induction drug when combined compared with their use as single agents; [9–10] one year BPAR incidence was an improved 8% [10]. We have now successfully used rATG/Dac as dual induction therapy in both kidney-alone [9–10] and simultaneous pancreas-kidney(SPK) [11] transplantation. We have also demonstrated that the addition of *anti*-CD25 to rATG more effectively delays the return of peripheral blood CD25+ cells [12].

The three induction antibodies, rATG [13–21], C1H [22–32], and daclizumab(Dac) [33–37] (or basiliximab in its place) [19,37–41], have each been shown to be effective as single induction agents. C1H and rATG have also shown a greater propensity for the development of regulatory T cells(T-regs) post-transplant [5,42–44], while Dac allows normal repopulation of T-regs post-transplant [45]. Our main goal in using dual antibody induction therapy was to bring the kidney transplant recipient even closer (through more effectively timed lymphodepletion) to an optimally immunosuppressed state, perhaps allowing further reduction in long-term maintenance drug dosing and continued corticosteroid avoidance [9–12,46–50]. While rATG contains antibodies to a wide variety of peripheral blood mononuclear (primarily T) cell epitopes and has been shown to reverse acute rejection [20], with possible preventive effects on preservation injury [14,18–19,21] and chronic rejection [15–16], C1H depletes T cells and other lymphoid subsets even more potently [5–8,22–26]. Thus, we thought to combine rATG with C1H as another dual induction therapy option.

In early 2006 we embarked on a prospective, single-center, open-label randomized trial of adult, primary kidney transplant recipients comparing two dual antibody induction strategies, rATG/Dac ($N = 100$) versus rATG/C1H ($N = 100$), with favorable BPAR and graft survival rates and no major differences in clinical outcomes being reported after a median follow-up of 38 mo post-transplant [51]. Here, we report updated results with a median follow-up of 96 mo post-transplant.

2. Materials and methods

Between February 2006 and April 2009, 200 adult recipients (ages 18–71 years) of either deceased donor(DD) or non-HLA identical living donor(LD) first kidney transplants were randomized in this open-label study immediately before transplantation. Most of these patients were non-highly sensitized, i.e., panel reactive antibodies (PRA) <20% for HLA class I and II antigens. Patient exclusionary criteria included: positive T-cell crossmatch, receiving an ABO incompatible kidney, receiving an organ transplant other than kidney, history of a non-indolent malignancy within the past 5 years, significant liver disease, having uncontrolled concomitant infections, recipient is pregnant or lactating, and recipient or donor is seropositive for the human immunodeficiency virus.

In the rATG/Dac arm (Group I) ($N = 100$), rATG(1 mg/kg) (Thymoglobulin®) was given intraoperatively, with equivalent additional doses given on days 2 and 3 post-transplant. The first dose of Dac(1 mg/kg)(Zenapax®) was also given intraoperatively, with one additional dose given 14 days later [9–10,51]. In the rATG/C1H arm (Group II) ($N = 100$), rATG(1 mg/kg) was given intraoperatively, and C1H(0.3 mg/kg) was given within 24 h post-transplant; no further dosing with either induction drug was planned. The center institutional review board approved the protocol, and all patients gave written informed consent prior to enrollment (Clinical Trials.gov ID: NCT01172418).

In both groups, tacrolimus was initiated at 0.1 mg/kg twice daily once renal function improved (serum creatinine concentration (Cr) <4 mg/dl absent dialysis), with a target (12 h) trough level of 4–8 ng/ml. Target enteric-coated mycophenolate sodium(EC-MPS) dosing was 720 mg vs. 360 mg twice daily for Groups I and II, respectively; one-half of standard daily EC-MPS dosing was targeted in Group II in order to avoid severe leukopenia previously seen with C1H [5–8]. Any withholding of EC-MPS for at least 2 weeks was documented along with reasons for withholding. Methylprednisolone was given intravenously at 500 mg/day for three days postoperatively followed by daily oral methylprednisolone or IV Solumedrol at 0.5–1 mg/kg/day during the first week primarily to avoid hypersensitivity reactions to the induction antibodies. No further corticosteroid use was planned after the first 7–10 days post-transplant.

The schedule of non-immunosuppressive adjunctive therapy was the same as in our previous protocols [1–10,35]. For cytomegalovirus(CMV) prophylaxis, all patients were treated immediately post-transplant with intravenous ganciclovir for 3 days, followed by daily valganciclovir orally for 3 mo with doses based on renal function. In donor CMV Ig+/recipient CMV Ig - combinations, valganciclovir was given for 6 mo postoperatively. In patients developing rejection that required corticosteroids or antilymphocyte therapy, intravenous ganciclovir or valganciclovir was reinstituted. Pneumocystis prophylaxis with trimethoprim-sulfamethoxazole was also given [1–10,35].

Histocompatibility typing of HLA-A, -B, and -DR loci, donor-specific crossmatching, PRA, and DSA monitoring (at baseline and times of suspected acute rejection) were determined serologically by the University of Miami Histocompatibility Testing Laboratory. All transplanted DD kidneys received hypothermic machine perfusion preservation with the RM3 Renal Preservation Machine using Belzer-MPS Machine Perfusion Solution as perfusate [52]. Tacrolimus trough levels were routinely compiled for each patient, performed by whole blood immunoassay, with blood samples taken 3/wk, 2/wk, and 1/wk during the first 3 mo, respectively, monthly for the next 9 mo, and then once every 2–3 mo thereafter. Dosing of all maintenance drugs at those times were recorded.

Delayed graft function (DGF) was defined as the requirement for dialysis during the first week post-transplant. All patients were prospectively followed for the incidence of biopsy-proven acute rejection (BPAR), biopsy-proven chronic allograft injury (CAI) (i.e., interstitial fibrosis/tubular atrophy), renal function (serum Cr and estimated glomerular filtration rate, eGFR) [53], new onset diabetes mellitus after transplant (NODAT), infections, graft loss, and death. BPAR was defined as a rise of 0.3 mg/dL or greater from the nadir Cr, accompanied by a confirmatory kidney transplant biopsy within 24 h of initiation of antirejection therapy; Banff criteria were used to determine rejection and CAI severity [54]. Protocol biopsies were not performed in this study. NODAT was defined according to the most recent ADA