Transplant Immunology 20 (2008) 32–42

Contents lists available at ScienceDirect

Transplant Immunology

journal homepage: www.elsevier.com/locate/trim

Comparison of four different immunosuppression protocols without long-term steroid therapy in kidney recipients monitored by surveillance biopsy: Five-year outcomes

Mysore S. Anil Kumar [a,*], M. Irfan Saeed [a], Karthik Ranganna [b], Gregory Malat [a], Nedjema Sustento-Reodica [c], Arjun M.S. Kumar [a], William C. Meyers [a]

[a] Department of Surgery and Division of Transplantation, Drexel University College of Medicine and Hahnemann University Hospital Philadelphia PA 19102, United States
[b] Department of Medicine and Division of Nephrology, Drexel University College of Medicine and Hahnemann University Hospital Philadelphia PA 19102, United States
[c] Department of Pathology, Drexel University College of Medicine and Hahnemann University Hospital Philadelphia PA 19102, United States

ARTICLE INFO

Article history:
Received 27 May 2008
Received in revised form 1 August 2008
Accepted 8 August 2008

Keywords:
Immunosuppression protocol
Kidney transplant
Steroid withdrawal

ABSTRACT

Induction and maintenance immunosuppression protocols with or without long-term steroid therapy in kidney transplant recipients are variable and are transplant center-specific. The aim of this prospective randomized pilot study was to compare 5-year outcomes in kidney recipients maintained on 4 different calcineurin inhibitor (CNI)-based immunosuppression protocols without long-term steroid therapy. Two hundred consenting patients who received kidney transplants between June 2000 and October 2004 were enrolled in 4 immunosuppression protocol groups, with 50 patients in each group: cyclosporine (CSA)/mycophenolate mofetil (MMF), CSA/sirolimus (SRL), tacrolimus (TAC)/MMF, and TAC/SRL. Induction therapy was done with basiliximab and methylprednisolone. Steroids were withdrawn on post-transplant day 2, and long-term steroid therapy was not used. Demographic characteristics among the four groups were comparable; approximately 50% of the recipients were African American and ≥80% of the kidneys transplanted were from deceased donors. Clinical acute rejection (CAR) was confirmed by biopsy and treated with intravenous pulse steroid therapy. Steroid-unresponsive CAR was treated with Thymoglobulin. Surveillance biopsies were performed at 1, 6, 12, 24, 36, 48, and 60 months to evaluate subclinical acute rejection (SCAR), chronic allograft injury (CAI), and other pathological changes per the Banff 2005 schema. The primary end point was CAR, and secondary end points were 5-year patient and graft survival rates, renal function, SCAR, CAI, and adverse events. In the first year post-transplant, the incidence of CAR was 18% in the CSA/MMF group, 8% in the CSA/SRL group, 14% in the TAC/MMF group, and 4% in the TAC/SRL group (CSA/MMF vs. TAC/SRL; $p=0.05$). The incidence of SCAR was 22% in the CSA/MMF group, 8% in the CSA/SRL group, 16% in the TAC/MMF group, and 6% in the TAC/SRL group (CSA/MMF vs. CSA/SRL and TAC/SRL; $p=0.05$). After the first year, the incidences of CAR and SCAR decreased and were comparable in all 4 groups. At 5 years post-transplant, cumulative CAI due to interstitial fibrosis/tubular atrophy (IF/TA), hypertension (HTN), and chronic calcineurin inhibitor (CNI) toxicity was observed in 54%, 48%, and 8% of the CSA/MMF group vs. 16%, 36%, and 12% of the CSA/SRL group vs. 38%, 24% and 6% of the TAC/MMF group vs. 14%, 25% and 12% of the TAC/SLR group (IF/TA: CSA/MMF vs. CSA/SRL and TAC/SRL; $p=0.04$, HTN: CSA/MMF vs. TAC/MMF and TAC/SRL; $p=0.05$, CNI toxicity: TAC/SRL and CSA/SRL vs. TAC/MMF; $p=0.05$). Five-year patient and graft survival rates were 82% and 60% in the CSA/MMF group, 82% and 60% in the CSA/SRL group, 84% and 62% in the TAC/MMF group, and 82% and 64% in the TAC/SRL group ($p=0.9$). Serum creatinine levels and creatinine clearances at 5 years were comparable among the groups. Our data show that the rates of CAR and SCAR in the first year post-transplant were significantly lower in the CSA/SRL and TAC/SRL groups and that cumulative CAI rates due to IF/TA and HTN at 5 years were significantly lower in the TAC/MMF, TAC/SRL, and CSA/SRL groups than in the CSA/MMF group. Despite significant differences in the incidences of CAR and SCAR and prevalence of different types of CAI at 5 years, renal function and patient and graft survival rates at 5 years were comparable among kidney recipients maintained on 4 different immunosuppression protocols without long-term steroid therapy.

1. Introduction

The present standard-of-care immunosuppression protocols in most transplant programs in the United States consist of induction with IL-2R or a lymphocyte-depleting antibody and maintenance with

* Corresponding author. Drexel University College of Medicine, MS 417, 5th Floor, Feinstein Bldg, Broad and Vine, Philadelphia PA 19102, United States. Tel.: +1 215 762 1856; fax: +1 215 762 1621.
E-mail address: akumar01@drexelmed.edu (M.S. Anil Kumar).

0966-3274/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.trim.2008.08.005

a calcineurin inhibitor (CNI) in combination with mycophenolate mofetil (MMF) or sirolimus (SRL) and long-term prednisone therapy [1–6]. Recent studies show that early withdrawal of steroids, that is, between 2 and 7 days after kidney transplant, is safe and equally efficacious compared with long-term steroid therapy but has the advantage of avoiding the wide-ranging side effects associated with long-term steroid administration [7–9]. Few prospective studies in kidney recipients compare different immunosuppression protocols with or without long-term steroid therapy [10–12]. The current CNI-based combination immunosuppression protocols are potent in decreasing acute rejections but are ineffective in preventing the development and progression of chronic allograft injury (CAI), which presently is one of the major causes of graft loss after a kidney is transplanted. Surveillance biopsy is a useful tool to monitor CAI in kidney transplant recipients. Additionally, CNI-based therapy has significant morbidity due to nephrotoxicity and other side effects that include malignancy, infection, and metabolic diseases [13,14]. Both MMF and SRL have antiproliferative properties and may be beneficial in delaying or minimizing CAI [15,16]. Prospective studies comparing the long-term outcomes of combination CNI-based therapy without long-term steroid therapy are lacking.

2. Objective

The aim of this pilot study was to prospectively compare and evaluate long-term outcomes in 200 kidney transplant recipients randomized into four different CNI-based immunosuppression protocols with early steroid withdrawal monitored by surveillance biopsy.

3. Patients and methods

This study was approved by the institutional review board of Drexel University College of Medicine and Hahnemann University Hospital (Drexel university project # 1000182). This study was registered as a randomized trial with the Cochrane Renal Group (# CRG 1106000095).

The protocol was designed to randomly assign 200 de novo kidney transplant recipients to one of 4 groups, with 50 patients per group and with each group receiving one of four immunosuppressive regimens: cyclosporine (CSA) with MMF, CSA with SRL, tacrolimus (TAC) with MMF, and TAC with SRL. Randomization was completed online using the first generator plan at Randomization.com (accessed at http://www.randomization.com). The study was open for randomization until 50 de novo kidney recipients were enrolled in each of the four groups for a total of 200 patients. All recipients in this study received transplants between June 2000 and October 2004. Selection criteria were as follows: recipients were older than 20 years of age, were able to sign an informed consent form, were HIV and HBV negative, had deceased and living donor kidneys, and were of any ethnicity. This report is an analysis of the subgroup of patients randomized into one of four groups of immunosuppression protocols treated without long-term steroid therapy. A cohort of patients in this study was reported previously to compare ethnicity [African American (AA) vs. non-African American (non-AA) kidney recipients] and to compare early steroid withdrawal and long-term steroid therapy in kidney transplant recipients but without comparing the outcomes of the four different immunosuppression protocols [9,17]. A cohort of the CSA/MMF group from the present study was described in a previous publication comparing early steroid withdrawal with long-term steroid therapy in kidney transplant recipients [18].

The present study is the first report of results comparing kidney transplant recipients randomized to four different CNI-based immunosuppression protocols with early steroid withdrawal.

3.1. Immunosuppression protocols and infection prophylaxis

All recipients were given induction therapy with 2 doses of 20 mg basiliximab on days 0 and 4 and 2 doses of methylprednisolone, 250 mg on day 0 and 125 mg on day 1. Steroid therapy was discontinued completely after the second dose of methylprednisolone [9].

TAC or CSA was initiated on day 1. TAC was initiated at 0.02 mg/kg body weight per day and the dose was increased rapidly to achieve trough blood levels of 15–18 ng/ml by day 4; these levels were maintained for 1 month. Beginning with the second month, the TAC blood levels were gradually reduced to 10 ng/ml by the end of 1 year. CSA was initiated at 3 mg/kg body weight per day, and the dose was rapidly increased to maintain C2 blood levels (cyclosporine blood levels 2 h after the dose) of 1000–1200 ng/ml at 1 month and then gradually tapered to maintain 700 ng/ml at 1 year. MMF was initiated on day 1 at 2 g/day in divided doses, and trough blood levels of mycophenolic acid were maintained between 1 and 3 μ/ml. SRL was initiated on day 4 at 2 mg/day; the dose was then adjusted to maintain trough blood levels of 5 to 10 ng/ml. During the initial study period, in the first 10 patients, clinical observations and surveillance biopsy results showed that with the above-described CNI blood levels, recipients in the CSA/SRL and TAC/SRL groups showed lower renal function and acute CNI toxicity confirmed by biopsy. After these clinical and biopsy findings were noted in the first 10 patients in each of the CSA/SRL and TAC/SRL groups, beginning 1 month after transplantation, the protocol was modified in subsequent patients to maintain lower blood levels of CSA and TAC. In the CSA/SRL and TAC/SRL groups, the daily doses of CSA and TAC were adjusted to maintain C2 blood levels of CSA of between 500 and 800 ng/ml and trough levels of TAC of between 5 and 9 ng/ml of blood. We did not use a loading dose of SRL, and initiation of SRL was delayed to day 4 to minimize wound-healing complications. Steroid therapy was discontinued after the second dose of methylprednisolone, and long-term steroid therapy was not used in these patients.

All participants except donor/recipient seronegative pairs received valganciclovir for prophylaxis for cytomegalovirus (CMV) infection. Trimethoprim-sulfamethoxazole was given for prophylaxis for *Pneumocystis carinii*. Both of these prophylactic agents were given for 100 days post-transplant.

3.2. Diagnosis and treatment of clinical acute rejection

Clinical acute rejection (CAR) was diagnosed as a persistently elevated level of serum creatinine that was 15% or more above baseline. All CARs were confirmed by percutaneous biopsy of the transplanted kidney. Patients with CAR confirmed by biopsy were treated with pulse doses of methylprednisolone: 1 g for 2 days or 500 mg for 4 days [9]. Recipients with steroid unresponsive rejections were re-biopsied and treated with Thymoglobulin (Genzyme Corp., Cambridge MA).

Table 1
Demographic characteristics of donors and recipients

Patient characteristics	CSA/MMF group	CSA/SRL group	TAC/MMF group	TAC/SRL group	*p* value
Recipients					
Age in years (mean±SD)	51±14	56±13	48±14*	59±12*	*0.05
Male gender (%)	35 (70%)	37 (74%)	34 (68%)	34 (68%)	0.08
African American (%)	25 (50%)	25 (50%)	27 (54%)	26 (52%)	0.9
Diabetes (%)	12 (24%)*	26 (52%)*	13 (26%)	23 (46%)*	*0.03
BMI (mean±SD)	28.0±4.8	28.2±5.8	29.8±8.4	27.1±5.3	0.88
HLA antigen mismatch (mean±SD)	4.0±1.9	4.1±2.0	4.0±2.1	4.1±1.8	0.9
Donor demography					
Deceased donors (%)	41(82%)	43 (86%)	44(88%)	43 (86%)	0.90
Expanded criteria donors (%)	12 (24%)	11 (22%)	11 (22%)	13 (26%)	0.89
Cold ischemia time in hours (mean±SD)	14±8*	15±6	16±8	17±8*	*0.04
Age in years (mean±SD)	42±18	47±11*	38±19*	45±25	*0.04
BMI (mean±SD)	26.1±6.3	28.0±6.1	28.6±15.3	27.2±13.6	0.88
Male gender (%)	29 (58%)	26 (52%)*	33 (66%)	34 (68%)*	*0.05

* Significant *p* value.