Prevention of acute rejection with antithymocyte globulin, avoiding corticosteroids, and delaying cyclosporin after renal transplantation

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Abstract

Background. Despite their well-known side-effects, corticosteroids (Cs) are currently used after kidney transplantation. Avoidance of Cs may improve patient quality of life and eventual long-term survival. We report on a regimen using antithymocyte globulin (ATG) and mycophenolate mofetil (MMF) for induction, and cyclosporin (CsA) plus MMF for maintenance treatment of recipients of primary kidney transplantation.

Methods. We studied 11 consecutive, non-sensitized renal transplant patients (nine cadaver and two living donors). Initial immunosuppression consisted of ATG (1.5 mg/kg/day, i.v.) given for 10 days and MMF (1.0 g/b.i.d.). CsA (8 mg/kg, in two divided doses) was started on post-operative day 11. Cs were only allowed in the case of MMF discontinuation, for the treatment of acute rejection, and in the event of recurrence of the primary glomerulonephritis.

Results. All patients completed the entire 10-day ATG course. Main side-effects included fever (>38°C) and serum sickness, observed in 73 and 27% of the patients respectively. The incidence of acute rejection was 27% (three of 11 patients). In two patients with acute rejection, serum sickness was concomitantly diagnosed and renal histology was partially compatible with immune-complex disease. The remaining patient had two episodes of low-grade rejection. All rejection episodes were rapidly reversed. Two patients (18%) were treated with ganciclovir for cytomegalovirus (CMV) infection. Two patients (18%) are currently receiving Cs for recurrence of the native glomerulonephritis and two rejection episodes respectively. All patients are currently alive with functioning kidneys (average follow-up of 8.4 months; average creatinine level of 128 μmol/l).

Conclusion. This pilot study suggests that ATG induc-tion in combination with MMF and delayed introduction of CsA, in the absence of Cs, is not well tolerated in recipients of kidney transplants. An earlier introduction of calcineurin inhibitors and/or a shorter course of ATG may reduce the incidence of fever and serum sickness secondary to ATG.

Keywords: antithymocyte globulin; corticosteroids; cyclosporin; immunosuppression; mycophenolate mofetil; side-effects

Introduction

The number of patients experiencing an acute rejection after kidney transplantation has decreased considerably during recent years. This is due to the effectiveness of novel associations of immunosuppressive drugs. Despite the well known side-effects of corticosteroids (Cs), these drugs continue to be included in such new combinations. We have previously reported on the effectiveness of an immunosuppressive regimen based on rabbit antithymocyte globulin (ATG), cyclosporin microemulsion (CsA), and mycophenolate mofetil (MMF), without Cs, in recipients of simultaneous kidney–pancreas transplants, in whom Cs administration had potentially detrimental effects [1]. Based on the very low (7%) incidence of acute kidney rejection in our first study, the aim of the present study was to extend our observation to kidney transplant recipients. In addition, we investigated whether delaying the introduction of CsA to the end of the ATG course would further improve outcome, since both Cs and CsA could interfere with the mechanism of action of polyclonal and monoclonal antilymphocyte globulins [2,3].

Subjects and methods

This study was approved by the Committee for Research on Human Subjects at the University Hospital of Nantes. Between November 1998 and April 1999, we enrolled 11
developed herpes labialis before CMV infection. One combinations must be 0% rejection remains unclear. No other bacterial or fungal infections were and lymphoproliferative disorders seem to be more ment; two of these also had serum sickness (on post- tion of most solid organ transplants.

Despite delaying CsA administration to day 11, two Similarly, the absence of Cs-induced anti-in

Immediate post-transplantation immunosuppression consisted of ATG and MMF. A 10-day ATG course (Thymoglobuline®, IMTIX-Sangstat, Lyon, France), at a starting intravenous dose of 1.5 mg/kg/day, was scheduled. Doses of ATG were then monitored and adjusted according to daily E-rosette test. ATG dose was adjusted to maintain the level of rosetting lymphocytes below 10% of the peripheral mononucleated cells. MMF (CellCept®, Hoffman La Roche, Neuilly-sur-Seine, France) was started orally at a dose of 1.0 g/b.i.d. This dose was decreased or discontinued in the case of adverse clinical or haematological events. CsA (Neoral®, Novartis, Rueil-Malmaison, France) was introduced on day 11 (after the end of the ATG course) at an oral dose of 8 mg/kg; in two divided doses. Doses of CsA were adjusted according to CsA blood trough levels, aiming for 150 ng/ml (Cyclo-Truc SP, Sorin, France). CsA was started only in case of MMF discontinuation following the ATG course, and in the case of acute rejection or recurrence of the primary glomerulonephritis. In patients suspected of experiencing an acute kidney rejection episode, a core renal biopsy was obtained to confirm the diagnosis and to graduate the histological features in accordance with the Banff classification [4]. Rejection episodes were treated with high-dose intravenous Cs (5, 5, 4, 3 and 2 mg/kg/day, over 5 consecutive days). Antiviral (herpes, cytomegalovirus (CMV)) prophylaxis was not given and no patient received granulocyte colony-stimulating factor to treat leukopenia.

Results

Follow-up ranged from 6 to 11 months (average 8.4). Despite delaying CsA administration to day 11, two patients (18%) required transient haemodialysis because of delayed graft function. The scheduled 10-day ATG course was given to all patients (an average of 24 vials per patient, ranging from 17 to 31). Low-grade fever was observed in all patients during ATG therapy with 73% having a temperature ≥ 38°C. Three patients (27%) developed a typical acute serum sickness and in two of them, renal impairment was involved. CMV infection was diagnosed in five patients (45%); however, only two patients required ganciclovir because of CMV disease. Three of the patients developed herpes labialis before CMV infection. One patient presented with a bacterial urinary tract infection. No other bacterial or fungal infections were observed. No patient experienced gastrointestinal side-effects, diabetes or malignancy.

Three patients (27%) received an anti-rejection treatment; two of these also had serum sickness (on post-operative day 10). Kidney lesions at the time of serum sickness and renal dysfunction were compatible with Banff 2b and Banff 2a rejection grade respectively (Figures 1 and 2). A rapid and complete normalization of renal function was observed in both patients after ATG withdrawal and OKT3/plasma exchange therapy. The patient with grade 2b rejection also required transient haemodialysis. As shown in Figure 1, a significant improvement of renal lesions was noted after anti-rejection treatment. No control biopsy was performed in the remaining patient. The third patient developed a borderline and grade 1a acute rejection episodes on post-transplant days 16 and 80 respectively. Both episodes were reversible with high-dose Cs.

All patients are currently alive and have functioning transplants. Only one patient has a serum creatinine level above 150 μmol/l. This patient has never experienced an acute rejection episode or acute serum sickness, but developed delayed graft function. The average serum creatinine of all patients is 128 μmol/l, ranging from 86 to 293. Only one patient has proteinuria >1 g/day, secondary to the recurrence of focal glomerular sclerosis. This last patient and the patient who was treated for two episodes of acute rejection are receiving Cs and tacrolimus treatment. Currently, two patients require treatment for hypertension. Throughout the follow-up period, MMF dosage was reduced in four patients because of leukopenia, it remained unchanged in six patients and was withdrawn in one patient.

Discussion

Despite not being aimed at efficacy, this pilot study suggests that the avoidance of Cs does not increase the incidence of acute rejection after primary renal transplantation. The need for anti-rejection treatment (27% of the patients) was similar (35%) to our historic controls receiving Cs, ATG induction, and delayed CsA [5]. None of these rejections impaired short-term renal function and/or induced permanent proteinuria. Similarly, the absence of Cs-induced anti-inflammatory effects was not associated with an increased incidence of delayed graft function (18%) or high levels of serum creatinine. On the other hand, patient clinical tolerance to ATG, without Cs and CsA, was poor (high incidence of fever and acute serum sickness) as compared to the pharmacovigilance profile of this drug when Cs and CsA are given concomitantly [6].

New immunosuppressive strategies have significantly reduced the incidence of acute rejection following kidney transplantation to as low as 20% [7–9]. Whether the actual primary end-point of these drug combinations must be 0% rejection remains unclear. Severe side-effects and adverse events such as diabetes and lymphoproliferative disorders seem to be more frequent than in the past. In addition, no true clinical tolerance has yet been achieved and chronic immunosuppression is still required for maintaining the function of most solid organ transplants.

Bacterial infections, gastrointestinal lesions, high
blood pressure, lipid abnormalities, glucose intolerance, excessive weight gain, cataracts, and osteoporosis are some of the well-known complications related to Cs treatment. Hence, immunosuppressive protocols aimed at avoiding Cs use may reduce the incidence of side-effects and eventually ameliorate the short- and long-term quality of life of the patients. On the contrary, avoidance of Cs may impair renal function by enhancing the ischaemia/reperfusion injury syndrome and/or by increasing the incidence of acute and chronic rejection. Our preliminary results suggest that a Cs-free regimen did not have a detrimental effect on renal graft function and survival (100% functional grafts). Moreover, no patient experienced gastrointestinal complication, systemic bacterial infection, or diabetes, suggesting the negative impact of Cs on patient outcome. Several recent studies have confirmed that kidney [10], kidney–pancreas [1] and liver [11] transplantation can be safely performed in the absence of Cs. Furthermore, in transplant animal models, Cs as well as CsA can block the immunosuppressive action of agents such as CTLA4-Ig [12] and anti-CD40L [13], and may have
a similar effect on ATG. Moreover, in vitro, Cs and CsA impede ATG-induced apoptosis of activated
T cells [2]. Whether ATG could be more efficacious in
the absence of Cs and CsA after human renal transplant-
ination remains to be determined. This pilot study
cannot provide the answer to this question because of
its inadequate statistical power and to the fact that
patient clinical tolerance was poor, requiring the pre-
mature termination of the trial. A high proportion of
patients developed fever and acute serum sickness (73
and 27% respectively). This unusually high incidence
of serum sickness may be partially explained by the
lack of Cs. As we previously reported, only 7% (two
of 28) of kidney/pancreas transplant patients experi-
enced serum sickness with a similar Cs-free,
ATG/MMF protocol. However, CsA was given from the
day of surgery [1].

In conclusion, because of increased toxicity, the
results of this pilot study do not favour the recom-
mendation of the avoidance of both Cs and CsA
during the induction treatment with ATG (i.e.
Thymoglobuline®) after renal transplantation. Further
studies will be required to determine whether an earlier
introduction of a calcineurin inhibitor and/or a shorter
ATG course will allow, in a Cs-free regimen, better
clinical tolerance, fewer type III hypersensitivity re-
actions, and optimal prevention of rejection.

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