Alemtuzumab Induction in Kidney Transplantation: Clinical Results and Impact on T-Regulatory Cells


ABSTRACT

Alemtuzumab (ALT), a humanized monoclonal anti-CD52 antibody, was introduced in solid organ transplantation as an induction agent. ALT associated with anticalcineurins has provided a low incidence of acute rejection episodes (ARE) and potential tolerogenic properties. We analyzed the clinical outcomes and effects on peripheral Treg of renal transplant recipients treated with ALT. Six-month data on kidney alone or kidney combined with pancreas or liver patients treated with ALT and tacrolimus (TAC) in standard doses were compared with those on renal transplant recipients of similar demography who were not treated with ALT. We evaluated patient and graft survivals, ARE incidence, hematological parameters, renal function, adverse events, and CD4+CD25+FoxP3+ T cells in peripheral blood. Demographics of recipients, donors, and transplants were similar in both groups. Mean HLA mismatch was slightly greater among ALT-treated patients (3.5 vs 2.5). No combined transplantation was performed in the ALT-untreated group. Patient and graft survivals were 100% without rejection or serious infections in both groups. ALT-treated recipients showed anemia and leukopenia in 3 patients as well as severe lymphopenia in 5 recipients, who partially recovered on day 90. Final mean plasma creatinine was 1.4 mg/dL, while calculated creatinine clearance was approximately 65 mL/min in both groups. Mean Treg cell percentage was higher among ALT-treated recipients than the comparative group or healthy controls (P < .05). In conclusion, renal transplantation results obtained using ALT with rigorous immunosuppressive therapy were excellent; serious adverse events and acute rejection were absent. The effect of the increased proportion of Treg cells must be evaluated with longer observation.

ALEMTUZUMAB (ALT; Campath, Schering) is a humanized monoclonal anti-CD52 antibody, recently introduced in solid organ transplantation as induction therapy. Its target, the CD52 molecule, is a glycoprotein expressed on approximately 95% of peripheral blood lymphocytes, natural killer cells, monocytes, macrophages, and thymocytes. ALT when used alone or associated with mTOR inhibiting drugs was not effective to obtain efficient immunosuppression, a conclusion supported by the high incidence of acute rejection episodes (ARE).1–4 many patients suffered C4d-positive humoral ARE.5 Nevertheless, anti-CD52 antibody combined with other immunosuppressive agents such as cyclosporine (Neoral, Novartis) or tacrolimus (Prograf, Astellas) with or without an antimeatabolite (MPA), either sodium mycophenolate (MPF; Myfortic, Novartis) or mycophenolate mofetil (MMF; Cellcept, Roche) may provide excellent outcomes with a low ARE incidence,5–7 without increasing the rate of adverse effects like infections or cancer. The main side effects of ALT are leukopenia and lymphopenia, which are severe and longlasting. Actually, B-lymphocyte counts return to normal levels within 3 to 12 months, but CD4+ and CD8+ T-lymphocyte counts may be depressed for 3 years.8

In relation to the effect of ALT induction on Treg, which seem to be crucial to develop tolerance, an increased proportion of these cells has been reported in recipients
induced with ALT, who were also treated with antiproliferatives and anticalcineurins, based on the comparison of Treg counts among treated versus nontreated patients, values in the pretransplantation period, and measurements in control volunteers. Also, in the context of renal transplantation, it has been shown that immunocompetent T cells with a memory phenotype are resistant to lysis following antibody-mediated T-cell depletion mediated by ALT. Some data suggest that in vitro these cells are sensitive to calcineurin inhibitors, which decrease interleukin 2 (IL-2) and interferon gamma production. These observations in aggregate reveal the complexity of factors influencing the balance between regulatory and reactive T cells among patients receiving multiple drug therapy.

The long-term benefit of using ALT and tacrolimus (TAC) in renal transplant recipients is far from being confirmed in at least 2 aspects: (1) its efficiency in terms of acute rejection sparing more than other antibodies commonly used for induction therapy; and (2) its possible tolerance-inducing effects. In fact, patients treated with ALT plus low-dose TAC (target trough blood levels of 4–7 ng/mL) and MPA still suffer an 18% incidence of biopsy-proven ARE despite the presence of 39% to 27% Treg measured at 60 to 240 days after transplantation. Furthermore, Kirk et al showed that all patients treated with 4 doses of ALT and deoxypergualin experienced ARE during the first month posttransplantation. In contrast, recipients treated with ALT and full doses of TAC (target level of 10 ng/mL) showed a low incidence of ARE (1%), but 45% of them experienced rejections following the anticalcineurin weaning, thus showing the persistence of an immunoreactive response among a high proportion of renal transplant recipients treated with the anti-CD52 antibody.

We have reevaluated the effect of immunosuppressive therapy including ALT and full-dose TAC plus MPA for maintenance immunosuppression in 8 consecutive unsensitized transplant recipients, including 2 retransplantations. We sought to evaluate the treatment efficacy in terms of patient and graft survivals, incidence of ARE, renal function, adverse events, and Treg status. CD4+CD25+FoxP3+ Treg cell responses measured during the repopulation period of ALT-treated recipients were compared with a group of renal transplant patients of similar demography and follow-up, who did not receive ALT for induction therapy.

**PATIENTS AND METHODS**

In 2005, ALT was introduced for the treatment of renal transplant recipients in our institution. In this communication we evaluated the outcomes after ALT treatment and immunosuppressive maintenance therapy including TAC at full dose and MPA with the intention to rapidly taper steroids. The study group included 8 kidney allograft recipients: male/female ratio was 6/2 and mean age was 51 years (range, 39–66 years). Two patients were recipients of second grafts and 3 received combined transplants: 2 renal and pancreas and 1 kidney and liver. Table 1 shows that 1 patient had 57% preformed HLA antibodies and that all recipients were CMV IgG positive. The mean HLA match was 1.65, while the mean HLA mismatch was 3.5. Donors were all deceased with a male/female ratio of 5/3 and a mean age of 36 years (range, 18–53 years). The mean cold ischemia time was 14.3 hours (range, 6–28 hours), and the mean plasma creatinine at donation was 0.9 mg/dL (range, 0.4–1.8 mg/dL). Two patients displayed delayed graft function (DGF), defined as requiring posttransplantation dialysis. ALT was initiated intraoperatively by a slow intravenous infusion of a 30 mg dose. Another 30 mg dose was given on day 4 posttransplantation in 3 recipients. Methylprednisolone was administered intravenously.

### Table 1. Demographic and Early Posttransplantation Outcome Variables in Recipients Treated With Alemtuzumab (ALT) and a Comparative Group Not Treated With Alemtuzumab (C)

<table>
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<th>Age (y)</th>
<th>Gender</th>
<th>Original Disease</th>
<th>PRA (%)</th>
<th>Age (y)</th>
<th>Gender</th>
<th>D/L</th>
<th>Renal/Pancreas/Liver</th>
<th>ABDR Mismatch</th>
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PRA = % preformed HLA antibodies; D/L = deceased or living donor; CIT = cold ischemia time; DGF = delayed graft function; IgA = IgA nephropathy; DM 1 = diabetes mellitus nephropathy.
during the first 4 days (500/250/125/60 mg/d) followed by oral prednisone withdrawn in 2 patients during the first week, and discontinued prior to week 12 in 2 other patients but maintained in 4 recipients. MMF or MPS (3 and 5 recipients, respectively) prescribed in standard doses were adjusted according to the blood leukocyte counts; either drug was discontinued when the WBC was below 3000/mm³. TAC was started on day 1 with the exception of 2 patients who suffered DGF and received the first dose on day 13 or 16. TAC administered at a dose of 0.10 to 0.15 mg/kg/d was thereafter adjusted to target levels of 12 mg/mL during the first month and approximately 8 to 10 mg/mL afterward. CMV prophylaxis initially included intravenous ganciclovir and thereafter val-ganciclovir was given to all patients for 3 to 6 months. Anti-infectious prophylaxis was provided by cotrimoxazole and nystatin at standard doses during the same period.

ARE was defined as an increase of serum creatinine of 0.3 mg/dL or greater from the nadir, which was unrelated to pre- or postrenal causes and confirmed by a renal biopsy. Hematological and biochemical parameters as well as renal function tests were evaluated daily during the first 2 weeks, twice a week during the following 14 days, thereafter weekly, and then every 2 weeks to 6 months. Creatinine clearance was calculated according to the Cockcroft-Gault formula. Screening for proteinuria was performed by dipstick or calculated based on the urinary protein and creatinine determination in a morning sample. TAC trough levels were determined by immunoassay (IMX, Abbott Park, Ill, United States).

In 7 patients, CD4+CD25+FOXP3+ T-cell counts were performed by flow cytometry (eBioscience Inc) with determinations performed at 2 months posttransplantation in 1 case, at 3 to 4 months posttransplantation in 5 other patients, and at 19 months posttransplantation in the remaining recipient. One patient did not consent to undergo the test.

A comparative group was formed by 7 recipients of kidney transplants who were not treated with ALT but otherwise received similar immunosuppression and were also followed for 6 months after transplantation. Among the ALT-untreated recipients, 2 received induction with thymoglobulin (Aventis) and 5 did not receive IL-2 receptor antagonists or any other induction. None of this cohort was sensitized. They were all maintained with steroids, cyclosporine, and MPA (4 cases) or azathioprine (2 cases). One patient was converted to low-dose TAC treatment associated with everolimus (EVL; Novartis, and another was converted to a calcineurin-free EVL-based treatment. Table 1 shows the demographics of the donors and recipients among the ALT-treated and -untreated recipients. All patients gave their informed consent to participate in the study; 1 patient treated with ALT refused to participate in the Fox3 determinations. The Student t test was used to compare samples.

RESULTS

There were no differences between the ALT-treated and comparative group regarding recipient and donor demographics such as age, gender, and recipient body mass index. Also, ALT recipients and controls were not different in cold ischemia time, mean HLA mismatch, donor plasma creatinine, recipient preformed antibodies, and DGF (Table 1).

Patient and Graft Survivals, Acute Rejection, and Clinical Outcome

ALT-treated patients. The 8 patients completed 6 months observation. The patient and graft survivals were 100%.

Two patients who displayed DGF gained normal renal function before the end of the first month. In all patients the diagnosis of ARE was not suspected given the stable renal, pancreas, or liver function. Exocrine and insulin production measured by lipase and amylase plasma concentrations and C-peptide or insulin blood levels were stable among combined pancreas/renal transplant recipients (data not shown). One patient who received a combined liver/renal transplant showed completely normal liver function. One renal biopsy, which was negative for rejection or viral infection (CMV or BK virus), was performed in another recipient who developed fever that lasted for the first 4 weeks following simultaneous kidney/pancreas transplantation. The microbiological and image studies were negative. The fever finally remitted in coincidence with antibiotics prescribed for an eventual diagnosis of sinusitis.

Comparative group. As in the ALT group, the patient and graft survivals were 100%. No rejection was suspected during the period. Three recipients displayed CMV infections that responded to specific treatment. Two patients displayed DGF. One of them did not recover renal function completely, maintaining a calculated creatinine clearance less than 30 mL/min during the observation period. Importantly, these 2 recipients were converted to either a low-dose TAC treatment associated with EVL or to a calcineurin-free EVL-based treatment.

Maintenance Immunosuppression

ALT-treated patients. Eight patients received TAC throughout the observation period without displaying evidence of either clinical neurotoxicity or nephrotoxicity. Mean and standard deviations of trough TAC levels at days 7, 28, 60, 90, and 180 were: 6.7 ± 1.9, 12.5 ± 4.3, 9.3 ± 1.9, 8.7 ± 1.9, and 7.6 ± 1.5, respectively. MPA doses were adjusted according to leukocyte count. In 4 patients, MPA was discontinued because of leukopenia. Steroids were eliminated in 4 patients according to the protocol, while they were maintained at low doses in second transplant recipients and in patients whose leukopenia prevented them from receiving MPA.

Comparative group. Five patients received cyclosporine throughout the observation period without showing any clinical signs of nephrotoxicity. C2 levels (data not shown) were maintained between 1100 and 1400 ng/mL during the first 2 months, and thereafter reduced to 800 to 900 ng/mL. Two patients converted to EVL presented EVL levels in the range of 3 to 5 ng/mL.

Hematological Adverse Events

ALT-treated patients. Table 2 shows the hematological changes that occurred in the first 6 months: moderate anemia (mean hematocrit increased from 27% to 37.4% from days 7 to 180), profound leukopenia in 3 recipients (mean WBC count approximately 3000/mm³ on days 60 and 90), and severe lymphopenia in 5 patients (absolute count = 0 or 2). On day 7, the mean lymphocyte count was...
24/mm³ increasing to 87/mm³ on day 28, 196/mm³ on day 60, 371/mm³ on day 90, and 918/mm³ on day 180.

Comparative group. Tables 2 and 3 show that in the whole 6-month period, there were lower values of hematocrit (NS), leukocytes (P < .05), and lymphocytes (P < .05 until day 90) among the ALT recipients when compared with the non-ALT-treated group. The comparative group showed less anemia and leukopenia, but the differences did not reach statistical significance. However, measurements performed around 4 months following transplantation, the time when regulatory T cells were measured, showed the total lymphocyte count (P = .028) and the CD4+ percentage (P = .001) and number (P = .012) to be significantly decreased in the ALT-treated recipients.

Treg Determinations in Both Groups

Three to 4 months following transplantation (the T-cell recovery phase), the percentage of CD4+CD25+FoxP3+ T cells was 19.9% ± 14.9% (range, 4.6%–42.3%) among patients treated with ALT and 4.1% ± 3.8% (range, 0%–11.5%) among recipients not treated with ALT (P = .031) and 3.1% ± 1.1% (range, 2.5%–4.6%) among healthy controls (P < .05 comparing ALT-treated versus healthy controls). Considering that the comparative group was not homogeneous and that 5 patients did not receive any antibody induction, we compared FoxP3+ T cells of this subgroup of recipients with those treated with ALT, observing that differences in the percentage of FoxP3 maintained their significance (P = .034). As expected, given the important total lymphopenia of the ALT group, the mean absolute counts of Treg were 4.1 ± 4.6, 17.2 ± 28.9, and 3.3 ± 0.8/mm³ among patients treated with ALT, treated without ALT, and healthy controls, respectively (NS). At the time when the FoxP3 determinations were performed, the mean leukocyte count was 4004 ± 2144/mm³ in the ALT group compared with 5162 ± 1985/mm³ in the comparative group.
ALT-treated patients. Mean plasma creatinine concentrations decreased from 2.6 ± 1.9 on day 7 to 1.4 ± 0.4 mg/dL on day 180. During the same time, calculated creatinine clearance increased from a mean of 51 ± 25 to 65.4 ± 13.8 mL/min (Table 2). No abnormalities in urinary protein excretion were observed (data not shown).

Comparative group. Table 2 shows that the mean plasma creatinine concentration decreased from 3.7 ± 1.8 on day 7 to 1.4 ± 0.6 mg/dL on day 180. During the same time, calculated creatinine clearance rose from a mean 29.9 ± 26 to 64.2 ± 25 mL/min. No abnormalities in urinary protein excretion were observed (data not shown). No statistical differences were observed between the ALT-treated and the comparative group relative to renal function parameters.

Serious Adverse Events

ALT-treated patients. No adverse effects were observed following ALT administration. An episode of profound venous thrombosis of the lower extremity contralateral to the organ implantation occurred in 1 case 1 month following renal transplantation. A subsequent ultrasound examination demonstrated resolution of the complication with subcutaneous anticoagulation. As already mentioned, 1 patient displayed low-grade prolonged fever during the first 4 weeks following combined kidney/pancreas transplantation. A relationship of this event to the study medication can only be assumed. No cases of CMV infection, new onset diabetes mellitus, or malignancies were seen during the study.

Comparative group. Three cases of CMV disease improved with specific therapy in this group. One patient developed a urinary fistula and lymphocele, both of which were corrected surgically. One recipient who had displayed DGF followed by stable renal dysfunction developed grade 2 chronic allograft nephropathy (Banff classification). The immunosuppression was switched to EVL plus low-dose TAC at 3 months posttransplantation. Another patient who showed DGF and subsequent low renal function (creatine clearance 24 mL/min) was converted to EVL plus low-dose TAC and steroids and MPA during the first month posttransplantation.

DISCUSSION

The search for new induction immunosuppressive protocols that have tolerogenic properties has been ongoing throughout the history of organ transplantation. Herein we have reported our experience with ALT, analyzing not only the clinical outcomes but also the presence of T regulatory cells (Tregs) supposedly relevant to long-term survival of transplanted organs.

The data presented in this article showed excellent 6-month outcomes in recipients of kidney alone a kidney combined transplants treated with the anti-CD52 monoclonal antibody. Patients who received ALT administered as a single 30 mg dose without or with a second 30 mg dose, depending on the presence or absence of DGF, were also treated with TAC in standard doses and, when the leukocyte count allowed it, an antimetabolite such as MPA. Patients were unselected and incorporated into the new therapy in a consecutive form, independent of the immunological risk. To compare immunological parameters, a group of recipients who were not treated with ALT was also examined. Nevertheless, there were 3 differences comparing the demographics of the ALT-treated vs comparative groups: (1) the comparative group did not receive combined grafts; (2) patients in the comparative group received cyclosporine and not TAC as the main immunosuppressive maintenance therapy; and (3) 5 recipients in the comparative group did not get antibody induction but 2 were treated with thymoglobulin. Four of the ALT-treated recipients must be considered to be high immunological risk: 1 was highly sensitized, while the other 3 were recipients of combined transplants (2 simultaneous renal/pancreas grafts and a second renal graft recipient who simultaneously got a liver graft). Only 1 recipient was highly sensitized in the comparative group.

The absence of ARE among the 8 ALT-treated patients throughout the first 6 months posttransplantation, the optimal renal function obtained in all patients, the relatively good compliance in the presence of mild leukopenia and lymphopenia, and the increase in Tregs are observations that lead us to speculate that the drug combination used in this study represented an important advance toward optimal immunosuppression. Four of 8 patients were steroid-free, while 3 remained under steroid therapy due to severe leukopenia which prevented us from using MPA. One last patient had to continue steroids at usual doses to avoid a recurrence of IgA nephropathy in a second transplant.

The leukopenia in the ALT recipients, which was more severe than in patients who did not receive ALT, forced MPA dose reduction or discontinuation, thus creating a situation often associated with a higher incidence of rejection or infection. Fortunately, that was not the case among ALT-treated recipients, who did not suffer rejection or severe infections during the study. As shown in Table 3, the control group displayed less anemia (P < .05) and did not show leukopenia or lymphopenia (P = .028). Thus, MPA prescription must be cautious in this cohort. Remarkably, CMV infection was present in 3 patients of the nonleukopenia control group and none of the ALT-treated recipients, probably due to lower adherence either to CMV prophylaxis or CMV antigenemia measurements in the comparative, non-ALT-treated group.

In relation to the use of anticalcineurin therapy as part of the maintenance immunosuppressive therapy during the first 6 months, TAC was dosed to obtain TAC trough blood levels (at day 28, the mean level was 12.5 ng/mL; range,
7.0–20.8 ng/mL), which were higher than those reported by Ciancio et al,⁷ who also reported a greater incidence of ARE. As planned, TAC trough levels were reduced afterward (7.6 ng/mL at 180 days) to prevent anticalcineurin nephrotoxicity. These TAC blood levels may represent the anticalcineurin concentration necessary to prevent ARE, perhaps due to sustained in vivo inhibition of IL-2 and interferon gamma production by memory T cells, which have been reported to be not abrogated by ALT.⁹,¹⁰ Among the comparative group, C2 cyclosporine levels were maintained within recommended values, namely 1436 ng/mL at 60 days and 844 ng/mL at 180 days (data not shown).

Confirming a previous report,⁷ patients treated according to this protocol showed a 5-fold increase in the mean percentage of CD4⁺CD25⁺FoxP3⁺ elements compared with recipients not receiving ALT or healthy controls among analyses performed on peripheral blood at approximately 120 days posttransplantation (19.9 vs 4.1; P < .05). Nevertheless, not all ALT-treated recipients showed the same degree of increase in CD4⁺CD25⁺FoxP3⁺: 3 displayed percentages twice those of healthy controls, but similar to untreated recipients. In 4 ALT-treated patients, the percentage increase was 10-fold. The follow-up of these patients may suggest whether these differences have predictive value for acute or chronic rejection or any relevant immunological outcome. Importantly, Ciancio et al⁷ reported that patients treated with basiliximab or thymoglobulin as induction therapy did not experience the same degree of increase in Treg cells measured as CD25⁺ T cells or FoxP3 copies/5000 CD3 cells. Recently, similar results have been obtained examining CD4⁺CD25⁺FoxP3⁺ T cells in transplant recipients treated with ALT, but followed for longer periods of time.¹²

This experience does not allow us to answer some basic questions about antibody induction therapies: (1) Do we get efficient tolerance when inducing with ALT? (2) Are peripheral FoxP3⁺ T cells significant in the clinical setting of organ transplantation to predict a tolerogenic state in a given patient? (3) In graft recipients treated with ALT, can anticalcineurin drugs be tapered at some time after transplantation to prevent nephrotoxicity without increasing the risk for ARE? Longer and larger studies using anti-CD52 antibodies must be designed to answer these questions.

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REFERENCES