Polyclonal Versus Monoclonal Induction Therapy in a Calcineurin Inhibitor–Free Immunosuppressive Therapy in Renal Transplantation: A Comparison of Efficacy and Costs

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ABSTRACT

Background. Induction therapy in renal transplantation reduces the incidence of acute rejection (AR) in expanded criteria donation (ECD) and donation after cardiac death (DCD). We compared the efficacy of Thymoglobulin (Sanofi-Aventis, Spain), ATG Fresenius (ATG-Fresenius, Spain), and Simulect (Novartis Farm, Spain) in a calcineurin-free protocol in ECD and DCD renal transplantation by evaluating patient survival, graft survival, and AR at 1 year and overall costs.

Methods. An observational retrospective study was performed using our database of 289 consecutive cadaveric ECD renal transplant recipients (n = 178) and DCD recipients (n = 111) from April 1999 to December 2011. Induction therapy consisted of Simulect, Thymoglobulin, and ATG Fresenius. Calcineurin-inhibitor (CNI)–free maintenance therapy consisted of mycophenolate mofetil or sodium and steroids.

Results. There were no differences in the patients' demographic characteristics or patient and graft survival. One-year AR rates were equivalent (ECD: 10%, 19.1%, 17.7% versus DCD: 14.3%, 7.1%, 16.7%). Leukopenia and thrombopenia were significantly more frequent in the ECD group treated with polyclonal induction. The average total cost of transplantation was higher in the ECD group but there were no significant differences in the average total cost between ECD and DCD: 39,970.31 ± 7,732€ versus 35,058.34 ± 6,801€ (P = NS).

Conclusion. Our study shows the same efficacy with polyclonal and monoclonal antibody induction and a CNI-free treatment regimen in ECD and DCD renal transplantation with no differences in overall costs at 1 year after transplantation.

INDUCTION therapy in renal transplantation is a specific and short-term treatment to reduce the incidence of acute rejection (AR) and prevent delayed graft function (DGF) after renal transplantation. Polyclonal (rabbit antithymocyte globulin) antibodies (Thymoglobulin [Sanofi-Aventis, Spain] or ATG Fresenius [ATG-Fresenius, Spain]) and basiliximab (Simulect [Novartis Farm, Spain]; interleukin-2 receptor monoclonal antibody) are the most common induction therapies used in renal transplantation, especially in transplantation from expanded criteria donors (ECD) and from donors after cardiac death (DCD). Both types of donation are associated with a high incidence of DGF.

These treatments appear to have similar efficacy in preventing DGF, but polyclonal antibody induction seems to be more potent and efficacious in preventing AR [1,2]. Additionally, the two therapies could differ in their safety profiles and some immunologic effects. Monoclonal antibodies are usually associated with fewer adverse effects because they only block the interleukin-2 receptor. Polyclonal antibodies are directed against different T and B lymphocyte epitopes, which seems to have positive effects on immunologic regulation and tolerance. Moreover, due to this polyclonality, these antibodies could have some secondary adverse effects (anemia, leukopenia, and

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0041-1345/14
http://dx.doi.org/10.1016/j.transproceed.2014.12.007

thrombopenia) and could also be associated with a higher incidence of viral infections and post-transplantation lymphoproliferative disease [3].

Prior studies of the cost-effectiveness of these therapies have shown that the specific costs of polyclonal antibodies are lower than those of monoclonal antibodies, although monoclonal antibody induction has a better safety profile and lower total cost in transplantation [4]. However, few studies have evaluated the overall costs of induction therapy and compared all the secondary variables associated with these induction regimens in ECD.

The aim of this study was to compare the efficacy of these three antibody induction regimens (Thymoglobulin, ATG Fresenius, and Simulect) in a calcineurin inhibitor (CNI)–free protocol in ECD and DCD renal transplantation by analyzing patient and graft survival and the incidence of biopsy-proven AR at 1 year. A secondary objective was to compare the overall costs of renal transplantation within the first year with these three induction strategies.

PATIENTS AND METHODS

Study Design and Population

We performed an observational retrospective study using our database and the medical records of 289 consecutive deceased-donor kidney transplantations performed in Hospital Clinic-University of Barcelona from April 1999 to December 2011. The inclusion criteria were low immunologic risk patients receiving a first or second renal transplant from an ECD (UNOS criteria) or a donor after cardiac death (uncontrolled DCD donors) treated with induction therapy (Basiliximab, Thymoglobulin, or ATG Fresenius) and scheduled for CNI-free maintenance therapy.

The parameters analyzed included recipient/donor age, gender, history of diabetes, number of previous transplantations, cold ischemia time, infectious complications requiring hospitalization, cytomegalovirus (CMV) disease, BK virus–associated nephropathy, malignant complications, major cardiovascular events, and cause of graft loss. One-year graft and patient survival rates were recorded.

Immunosuppressive Therapy and Anti-infective Prophylaxis

Expanded Criteria Donation. Induction therapy consisted of basiliximab (20 mg × 2 doses), ATG Fresenius antibodies (5 daily doses of 3 mg/kg adjusted according to lymphocyte count), or Thymoglobulin (rabbit antithymocyte globulin) antibodies (5 daily doses of 1.25 mg/kg adjusted according to lymphocyte count), depending on the potential recipient's immunologic history and current panel-reactive antibody (PRA) titers. Methylprednisolone was administered intravenously with an intraoperative dose of 500 mg, 125 mg on the second day, and 0.5 mg/kg on the third day after surgery and was then tapered to an oral 20-mg prednisone dose at discharge. Mycophenolate mofetil (MMF) or sodium (2000 mg or 1440 mg) was initiated on the day of surgery, followed by 1000 mg or 720 mg every 12 hours. Since 2002, sirolimus or everolimus was initiated on the fifth day after surgery at a dose of 2 mg every 24 hours and was then adjusted according to trough concentrations (target trough levels approximately 10 ng/mL).

Donation After Cardiac Death. The same induction strategy was used in DCD renal transplant recipients as in ECD. Three months after allografting, maintenance immunosuppression included MMF or sodium (1000–1500 mg/d), everolimus or sirolimus (trough level 5–8 ng/mL), and prednisone (5 mg/d). In both groups, immunosuppressant therapy was adjusted during the follow-up period, based on biopsy data or clinical events. All rejection episodes were confirmed by percutaneous renal biopsy.

All patients received CMV prophylaxis (valganciclovir) for 3 months postoperatively, regardless of their CMV serostatus. Oral *pneumocistis carinii* prophylaxis (trimethoprim/sulfamethoxazole 400/80 mg/d) was administered for 6 months postoperatively in all patients.

Laboratory Determinations

Kidney graft function was evaluated by recording creatinine and proteinuria levels at 3, 6, and 12 months. We also recorded the incidence of leukopenia (<2000 white blood cell count/mm^3) and thrombopenia (<90,000 platelets/mm^3) within the first month after transplantation.

Pharmaco-economic Analysis

The following data were recorded for the pharmaco-economic analysis: surgery costs without counting the extraction cost, hospitalization and re-hospitalization costs, dialysis costs, and the cost of all therapeutic and prophylactic medications. We also analyzed the number and costs of laboratory determinations (clinical chemistry, hematology, and drug monitoring), microbiological investigations, imaging tests, and outpatient visits during the first year. Net ex-factory prices were taken as the per unit reference prices of all medical products, and the official price listing provided by our hospital administration was used for all diagnostic and hospitalization variables, without considering any price reduction or promotional pricing.

Statistical Analysis

A descriptive statistical analysis was performed. Comparisons between groups were performed using the Student *t*-test, Mann-Whitney U test, χ^2 test, Wilcoxon Z-test, and analysis of variance, as appropriate, and correlations were explored using Spearman's coefficient. All statistical analyses were performed with SPSS version 17.0 (SPSS System, Chicago, Ill, United States, 2008).

RESULTS

Descriptive Evaluation of Recipient and Donor Characteristics

A total of 178 patients received an ECD renal transplant and 111 a DCD renal transplant. In the ECD group, 5.6% (10 patients) received Thymoglobulin, 11.8% (21 patients) ATG Fresenius, and 82.6% (147 patients) Simulect. In the DCD group, 82% (91 patients) received Thymoglobulin, 12.6% (14 patients) ATG Fresenius, and 5.4% (6 patients) Simulect. There were no differences in the recipient/donor characteristics in the ECD or DCD groups in the three different induction agents (Table 1).

Clinical Follow-up

Patient and Graft Survival, Acute Rejection Episodes and Complications. In ECD transplantation, 1-year patient survival was 100% in the polyclonal induction group versus 96.6% in the basiliximab group (P = NS). One-year graft survival censored for death was 90% in the Thymoglobulin group, 85.7% in the ATG group, and 93.1% in the Basiliximab group (P = NS). In DCD transplant recipients, 1-year patient survival was 100% in the three induction