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Cost-Effectiveness Analysis of Everolimus versus Mycophenolate in Kidney Transplant Recipients Receiving No Pharmacological Prophylaxis for Cytomegalovirus Infection: A Short-Term Pharmacoeconomic Evaluation (12 Months)

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ABSTRACT

Background: Modern immunosuppressive regimens, although associated with improved 1-year graft survival, are associated with adverse effects, including opportunistic infections, diabetes mellitus after transplantation, cardiovascular complications, and de novo malignancies. **Objectives:** To determine the short-term (12 months) cost-effectiveness of everolimus (EVR) versus mycophenolate sodium (MPS) in kidney transplant recipients receiving induction therapy, tacrolimus, prednisone, and no prophylaxis for cytomegalovirus infection. **Methods:** A Markov state transition model was designed. Data from a single-center prospective trial were used along with data from the center's medical bills database. The target population comprised adults with low immunological risk submitted to first ABO-compatible transplantation with kidneys recovered from living or deceased donors. The time horizon was 12 months. The interventions included tacrolimus and prednisone plus a single 3-mg/kg dose of rabbit antithymocyte globulin (ATG) and EVR or basiliximab (BAS) and EVR or BAS and MPS. The clinical outcomes considered for this analysis were cytomegalovirus infection/disease, acute rejection, graft dysfunction, surgical complications, graft loss, and life-years gained. **Results:** ATG/EVR was cost-saving compared with BAS/MPS on all evaluated outcomes; BAS/EVR outperformed BAS/MPS on most of the evaluated outcomes. Results were confirmed by sensitivity analysis. **Conclusions:** Compared with MPS, EVR is an alternative immunosuppressive agent that is able to provide resource-saving to the health care provider with effectiveness gains for the patient.

Keywords: cost-effectiveness, everolimus, mycophenolate, prophylaxis, renal transplantation.

Introduction

Treatment for end-stage chronic kidney diseases, including dialysis or transplantation, is generally funded by public health insurance in developing countries [1,2]. For kidney transplant recipients, immunosuppressive drugs constitute more than two-thirds of follow-up costs [3]. Modern immunosuppressive regimens, although associated with improved 1-year graft survival, are associated with adverse effects, including opportunistic infections, diabetes mellitus after transplantation, cardiovascular complications, and de novo malignancies [4].

Cytomegalovirus (CMV) infection/disease is the most frequent opportunistic infection, being associated with increased morbidity, mortality, and costs after kidney transplantation [5,6]. Because of the high efficacy for the prevention of acute rejection of modern immunosuppressive regimens, proper management of CMV infection/disease is mandatory. The two alternative strategies to manage CMV infection, universal prophylaxis and pre-emptive therapy, although relatively effective, are associated with increased costs and utilization of human resources [7,8].

Recent data have shown that the use of mammalian target of rapamycin inhibitors is associated with reduced incidence of CMV infection, with or without the use of pharmacological prophylaxis [9]. In this context, the objective of this study was to determine the cost-effectiveness of three immunosuppressive regimens in low to moderate immunological risk renal transplant

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recipients, receiving no CMV pharmacological prophylaxis under the perspective of the Brazilian public health care system. It is important to note that the study was conducted in the major reference center for kidney transplantation in Brazil (Hospital do Rim), which performed approximately 20% of the kidney transplants in the country. Therefore, the target population of this study is a clear representation of the patients who are usually found on daily practice around the country [10]. The results of this study can be of great relevance for decision makers because the choice of immunosuppressive regimen can be a major point of morbidity-related cost savings [11].

Methods

Setting and Location

The Brazilian health care system (*Sistema Único de Saude* [SUS]) provides universal coverage to every Brazilian citizen. The country also has the second largest national transplant program, second only to the United States. About 8000 solid organ transplants are performed per year, 5556 of which are kidney transplants. More than 90% of these transplants are under the SUS system, making it the world's largest public program in this therapeutic area. The SUS coverage includes transplant procedures and follow-up care, including a lifelong supply of immunosuppressive medications [12]. Hospital do Rim, located in São Paulo, is a large kidney transplant center that treats patients from all regions of Brazil and performs about 900 kidney transplants per year. Similar to what is done in a national transplant program, more than 90% of these activities are performed through the SUS [10].

Target Population

The modeled patient population comprised adults with low immunological risk submitted to first ABO-compatible transplantation with kidneys recovered from living or deceased donors [Supplemental material, Table1]. Clinical data from a prospective trial titled "Efficacy and safety of induction strategies combined with low tacrolimus exposure in patients submitted to kidney transplantation receiving everolimus or sodium mycophenolate" and registered on the Clinical Trials database as NCT01354301, involving 288 de novo kidney transplant recipients between July 11, 2011, and May 4, 2013, with a time horizon of 12 months [9], were used as inputs to the economic model and to determine the cost-effectiveness of the comparators during the first year after renal transplantation.

Study Perspective

This study was developed from the perspective of the Brazilian public health care system (SUS), considering the resource use guidelines and costs from the transplant center. Although data were based on a single center, the guidelines and associated treatment costs were representative of the whole SUS, because guidelines and reimbursement costs are defined by federal policies. Besides that, the aforementioned transplant center performs approximately 20% of all renal transplants in Brazil. Thus, results can be generalized to the whole of SUS.

The perspective was chosen on the basis of the context of the Brazilian transplantation system, where most of the solid organ transplantations are performed under the SUS. This is the most relevant perspective to be evaluated.

Comparators

Three immunosuppressive regimens were evaluated. In the first group (rabbit antithymocyte globulin/everolimus [rATG/EVR], n = 85), patients received r-ATG (single 3-mg/kg dose; Sanofi) as induction therapy, tacrolimus (TAC, 0.05 mg/kg twice a day; Libbs) adjusted to maintain whole blood trough concentrations below 5 ng/ml, EVR (1.5 mg twice a day; Novartis) adjusted to maintain whole blood trough concentrations between 4 and 8 ng/ml, and prednisone. In the second group (basiliximab/everolimus [BAS/EVR], n = 102), patients received BAS (20 mg on days 0 and 4; Novartis), TAC doses (0.1 mg/kg twice a day) adjusted to maintain whole blood trough concentrations between 3 and 8 ng/ml for the first 3 months and then reduced below 5 ng/ml, EVR doses (1.5 mg twice a day) adjusted to maintain whole blood trough concentrations between 4 and 8 ng/ml, and prednisone. In the third group (basiliximab/mycophenolate sodium [BAS/MPS], n = 101), patients received BAS (20 mg on days 0 and 4), TAC doses (0.1 mg/kg twice a day) adjusted to maintain whole blood trough concentrations between 6 and 8 ng/ml, MPS (720 mg twice a day; Novartis), and prednisone. Changes in the initial randomized immunosuppressive therapy were permitted either because of lack of efficacy or adverse events. All drugs were started within 24 hours of graft revascularization. None of these patients received any pharmacological prophylaxis for CMV infection. Pre-emptive strategy using pp65 antigenemia test was used for the first 6 months after transplantation.

When the core study was first designed, our hypothesis was that a single dose of ATG induction therapy or BAS in combination with low-dose TAC, EVR, and prednisone would result in comparable efficacy (biopsy-proven acute rejection) observed in patients receiving the standard regimen with TAC/MPS/prednisone but with a better safety profile. The rationale for the use of a single dose of ATG induction therapy was based on several previous studies that showed effective and safe results [13,14].

We anticipated that a single 3-mg/kg dose would provide protection against acute rejection during the first weeks after transplantation without increasing the risk of infections. The rationale for reduced exposure to TAC was based on the results of the Symphony trial [15] showing that targeting TAC concentrations between 3 and 7 ng/ml results in excellent efficacy and renal function. This regimen could also result in superior safety, namely, 1) lower incidence of viral infections, including CMV, herpes, and poliomavirus infection; 2) lower incidence of bacterial and fungal infections; 3) lower incidence of diarrhea; and 4) comparable renal function. This safety profile may be even better in those patients with EVR.

Time Horizon

Most of the possible complications arise in the first year after the graft transplantation. The relevant factors that impact long-term follow-up were evaluated in this analysis such as acute rejection, CMV infection/disease, surgical complications, and events related to treatment discontinuation. After one year of kidney transplant, the prevalence of these events is low and therefore less is the impact in graft and patient survival. For this reason, a more conservative time horizon (12 months) was chosen in order to observe this period which is the most relevance for long term follow up.

Discount Rate

No discount rate was applied because the time horizon was not more than 1 year.

Outcomes and Measurement of Effectiveness

The clinical outcomes considered for this analysis were CMV infection/disease, acute rejection, graft dysfunction, surgical complications, graft loss, and life-years gained. The economic outcomes contemplated in the analyses were direct medical costs, including medical resources used directly for patient treatment,