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Generic formulation of Cyclosporine A, Equoral®, in *de novo* kidney transplant recipients: Five-year follow-up

Mariusz Niemczyk[ABCDEF], **Leszek Pączek**[ADEF]

Department of Immunology, Transplant Medicine, and Internal Diseases, Medical University of Warsaw, Warsaw, Poland

Summary

Background: Equoral® is a generic formulation of Cyclosporine A (CsA), which is significantly cheaper than the original medicine. Our center participated in the clinical trial designed to evaluate the efficacy and safety of Equoral® in kidney transplant recipients in the first 9 months after a transplant procedure. The aim of our paper is to present the 5-year follow-up of patients who participated in the study and were monitored in our center.

Material/Methods: We performed intention-to-treat retrospective analysis of 20 *de novo* kidney transplant recipients who received Equoral®-based immunosuppressive regimen and were monitored in our department for 5 years after transplantation.

Results: The 5-year patient and graft survival was 90%, and the frequency of acute rejection was 15%. In 80% of patients, the initial immunosuppressive regimen had to be changed.

Conclusions: In our group of kidney transplant recipients, immunosuppression based on generic formulation of CsA had excellent 5-year patient and graft survival and effectively prevented acute rejection episodes. However, most patients needed modification of the initially administered immunosuppressive regimen.

Key words: **cyclosporine A • Equoral® • follow-up • graft survival • kidney transplantation • patient survival**

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Author's address: Mariusz Niemczyk, Department of Immunology, Transplant Medicine, and Internal Diseases, Medical University of Warsaw, Nowogrodzka 59 Str., 02-006 Warsaw, Poland; e-mail: mariuszniemczyk@wp.pl

Background

Cyclosporine A (CsA) is an immunosuppressant that has significantly improved results of organ transplantation since the 1980's. Equoral® (TEVA, Czech Republic) is a generic formulation of CsA, which has been available in Poland since 2002. Its bioequivalence to the innovator drug was proven in healthy volunteers [1] and its pharmacokinetics in stable renal transplant recipients was reported as equivalent to the original CsA formulation [2,3]. A paper reporting clinical experience with Equoral® was published in 2004 [4]; however, only 10 patients were included in that report, the follow-up period was quite short (6 months), and no comparison to the original formulation of CsA was included. The 6-month retrospective results of Equoral® in *de novo* kidney transplant recipients were also presented by Spasovski et al. [5]. Additionally, 2 trials confirmed that Equoral® is fully comparable to the original CsA in stable renal transplant patients in a 6-month period [6,7].

From the Polish National Health Found, in 2010 Equoral® was approximately 30% cheaper compared to the original formulation of CsA; therefore, the potential economic benefits of using the generic formulation of CsA are substantial.

A clinical trial concerning safety and efficacy of Equoral® in *de novo* renal transplant recipients was conducted in 3 transplant centers in Poland, including our department [8]. The aim of this paper is to present results of 5-year follow-up of patients included into the study in our department.

Material and Methods

The study protocol, inclusion and exclusion criteria, and short-term results were published previously [8]. We performed the intention-to-treat (ITT) retrospective analysis of patients included into the study and monitored in our department for 5 years after transplantation. We were interested mainly in hard end points: 5-year graft and patient survival. Additionally, we collected data concerning frequency of acute rejection, the need for conversion of the immunosuppressive regimen, and kidney function. The glomerular filtration rate (GFR) was calculated according to the Cockcroft-Gault formula.

Kidney transplantation was performed in 22 patients included into the trial and treated in our department. Two patients, who moved to other transplant centers in the first year after transplantation, were excluded from our analysis. The remaining 20 patients were included into our ITT analysis. Their characteristics are presented in Table 1.

Table 1. Characteristics of analyzed group.

Mean age at transplantation (range); years	45.7 (28–61)
Male/female; n(%)	14 (70%)/6 (30%)
Reason of ESRD; n(%)	• Chronic glomerulonephritis, 9 (45%) • Interstitial nephropathy, 4 (20%) • ADPKD, 2 (10%) • Diabetic nephropathy, 2 (10%) • Rapidly progressive glomerulonephritis, 1 (5%) • Unknown, 2 (10%)
First transplant; n(%)	20 (100%)
Donor cadaveric/living; n(%)	20 (100%)/0 (0%)
Donor male/female; n(%)	13 (65%)/7 (35%)
Donor mean age (range); years	42.3 (22–71)
Mean cold ischemia time (range)*; hours	26.67 (4.27–38.5)
Mean warm ischemia time (range)**; minutes	35 (21–65)

ADPKD – autosomal dominant polycystic kidney disease; * data for 14 patients; ** data for 16 patients.

Results

The 1-year patient and graft survival was 100%. During the first 5 years after transplantation, 2 patients died with functioning graft (1 due to malignancy and 1 due to septic complications). No other patient lost the graft. Therefore, the 5-year patient and graft survival was 90%. There were 3 acute rejection (AR) episodes in 3 patients (15%). AR occurred in the first year post-transplant in 2 patients, and in the third year after transplantation in 1 patient. All acute rejection episodes were successfully treated with IV steroids. The mean GFR after 1 year post-transplant was 59.3 mL/min (range 22.1–119.4 mL/min) (n=20), and after 5 years was 61.88 mL/min (range 33.4–86.1 mL/min) (n=18).

Change of the initial immunosuppressive regimen was needed in 16 (80%) patients, including 3 patients who needed multiple conversions.

Table 2. Reasons for conversions from azathioprine to mycophenolate mofetil/sodium (n=16).

Reason	N (%)
Hyperuricaemia – to enable introduction of allopurinol	3 (18.75%)
Acute rejection	3 (18.75%)
Anemia	3 (18.75%)
CsA nephrotoxicity – to enable reduction of CsA dose	2 (12.5%)
Gingival hyperplasia - to enable reduction of CsA dose	2 (12.5%)
Low CsA trough level	1 (6.25%)
Transplant nephropathy	1 (6.25%)
Reason unknown	1 (6.25%)

CsA – cyclosporine A.

Conversions were made in the first year post-transplant in 8 patients, and the other conversions were made later. In all converted patients, during the first conversion, azathioprine was changed to mycophenolate due to reasons specified in Table 2. Subsequently, conversions to tacrolimus were made in 2 patients with gingival hyperplasia, and in 1 case conversion to sirolimus was made due to pulmonary malignancy. Ultimately, 5 years post-transplant, only 4 patients (20%) were treated according to the initial immunosuppressive regimen. Among other living patients, 12 received immunosuppression consisting of steroid, CsA, and mycophenolate, and the remaining 2 were on steroid, tacrolimus, and mycophenolate.

Discussion

In our patients, the 1-year patient and graft survival were both 100%, and the 5-year patient and graft survival were both 90%. The rate of acute rejection at 5 years post-transplant was 15%. Unfortunately, this was only a single-arm study, but comparisons to previously published 5-year results obtained with original formulation of CsA [9–12] show that results with Equoral® are at least not inferior.

It should be emphasized that up to 80% of patients needed change of the initial immunosuppressive regimen consisting of steroid, azathioprine, and CsA. After 5 years post-transplant, two-thirds of patients living with a functioning graft received steroid with CsA and mycophenolate as the immunosuppressive therapy. As every conversion of immunosuppression carries the risk of acute rejection, it should be considered whether Equoral® should not be given with mycophenolate rather then with azathioprine in the primary immunosuppressive therapy after kidney transplantation.

Our study had several limitations. It was a retrospective, single arm analysis. The group was quite small and selected according to inclusion and exclusion criteria that might have favorably impacted the results. However, according to our knowledge, this is the first report on 5-year follow-up of patients receiving Equoral®-based primary immunosuppression after their first cadaveric kidney transplantation.

Conclusions

In our group of kidney transplant recipients, immunosuppression based on generic formulation of CsA was associated with excellent 5-year patient and graft survival and effectively prevented acute rejection episodes. However, most of patients needed modification of the initially administered immunosuppressive regimen.

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