

USE OF EQUORAL® IN *DE NOVO* RENAL TRANSPLANT RECIPIENTS

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This paper presents our experience to date with using a cyclosporine formulation Equoral® (IVAX Pharmaceuticals) together with mycophenolate mofetil plus a steroid immunosuppressive regimen in the treatment of *de novo* renal transplant recipients.

Ten cadaveric donor renal transplant recipients of mean age 51.6 years (range 37–66) were followed up over 6 months for the development of rejection attacks and side effects. All patients received prednisolone, mycophenolate mofetil (1 g/day during the first 5 days posttransplant and then 20 mg/kg/day) plus cyclosporine (3 mg/kg/day).

Biopsy proven acute rejection episodes were observed in 2 out of 10 patients (20%). Six months patient as well as renal graft survival rate was 100%. The development of graft function was immediate after transplantation. The mean serum creatinine levels were gradually decreased. Over the 6-month posttransplant period, the function of the graft was satisfactory and stable. The majority of observed adverse events were those commonly reported with the use of cyclosporine and they resolved with a reduction in cyclosporine dose. Equoral® treatment demonstrated an acceptable safety profile with maintenance of adequate renal function without incidence of malignancy/lymphoproliferative disease or serious infections.

In conclusion, Equoral® plus mycophenolate mofetil immunosuppression seems effective and safe on terms acute rejection rates, patient and renal graft survival rates and side profiles.

INTRODUCTION

Cyclosporine A is a neutral lipophilic cyclic undecapeptide, produced as a fungal secondary metabolite. It represents a group of the most potent immunosuppressants termed calcineurin inhibitors due to their ability to inhibit calcineurin phosphatase, the essential enzyme in the process of the gene transcription for interleukin-2 (IL-2) and other proinflammatory cytokines¹. The inhibition of calcineurin phosphatase results in suppression of the activation of T cells chiefly but also other molecules involved in cell-mediated immunity. The aftermath of this action is interruption of the downstream sequence of events leading to allograft rejection. Thus, cyclosporine has immunosuppressive properties and has a proven place as first line therapy in the prophylaxis and treatment of transplant rejection. Twenty years ago, cyclosporine became available in many transplant centres achieving 80% to 90% 1-year cadaver graft survival results.

The first original cyclosporine formulation Sandimmune® was introduced into clinical practice two decades ago and was characterised by high inpatient and outpatient pharmacokinetic variability with poor bioavailability in many patients. A novel microemulsion formulation Neoral® was therefore developed to circumvent these problems. The microemulsion has self-

emulsifying properties that enhance bioavailability and reduce pharmacokinetic variability between and within patients^{2–4}.

Equoral® (IVAX Pharmaceuticals, Czech Republic) is a generic cyclosporine for Neoral® an original patented formulation, that gives microdispersion in aqueous environments. Due to the hydrophilic gel-like character of the created microdispersed particles the system circumvents the intestinal mucus layer, adheres to the intestinal wall and ensure a sufficient concentration gradient of active substance resulting in increased bioavailability. Several bioequivalence studies with a total of 278 healthy volunteers and one pharmacokinetic conversion study with 70 stable adult renal transplant recipients were performed to compare the brand leader Neoral® with Equoral®. The results of these studies are converted to bioequivalence criteria and they have demonstrated that both drugs, Equoral® and Neoral® are bioequivalent and interchangeable in stable renal transplant recipients^{5–7}. This study presents our experience in *de novo* renal transplantation in terms of the safety and efficacy of Equoral® that was used as part of a triple-drug regimen.

Table 1. Patient demographics

Total number of patients		10
Sex	Females	0
	Males	10
Age	Mean \pm SD	51.6 \pm 10.9
	Median	51.5
	Min-Max	37–66
Height	Mean \pm SD	175.4 \pm 9.2
	Median	173.5
	Min-Max	163.0–198.0
Weight	Mean \pm SD	75.4 \pm 14.0
	Median	73.0
	Min-Max	60.0–111.0
Donor type	Living	0
	Cadaveric	10

PATIENTS AND METHODS

The recipient group included 10 males and no females mean age of 51.6 years (range 37–66). The patients after their first renal transplantation from a cadaver donor were treated using routine generally accepted triple-drug maintenance immunosuppressive regimen consisted of cyclosporine, mycophenolate mofetil, and corticosteroids.

Before transplantation surgery, Equoral® was given as a single oral dose at an initial dose of 3 mg/kg, followed by a dose of 5 mg/kg on the first postoperative day. The maintenance Equoral® therapy was begun on the second day after surgery at a dosage 3 mg/kg divided into two separate doses administered at 12-hour intervals. The daily doses were individualized per patient to achieve whole blood concentrations within the following ranges: 300–400 ng/ml during first six days after transplantation; 200–300 ng/ml at 7–30 days and 150–250 ng/ml at 2–6 months.

Mycophenolate mofetil was begun 24 hours after surgery at an initial dose of 1000 mg in two divided doses, followed from day 5 by dosage 20 mg/kg administered in two daily doses every 12 hours. Methylprednisolone was given intravenously at a dose 500 mg on the day of operation, 125 mg on the first postoperative day and maintained at gradually decreasing doses of prednisolone: 30 mg by day 2; 20 mg by day 15; 15 mg by month 3; and 10 mg by month 6. Acute rejection episodes were first treated with methylprednisolone. Renal biopsy was not performed routinely but reserved only for selected cases. Differential diagnosis with non-immunological causes of graft dysfunction was carried out by means of duplex Doppler scanning ultrasonography. Graft loss was defined as death or return

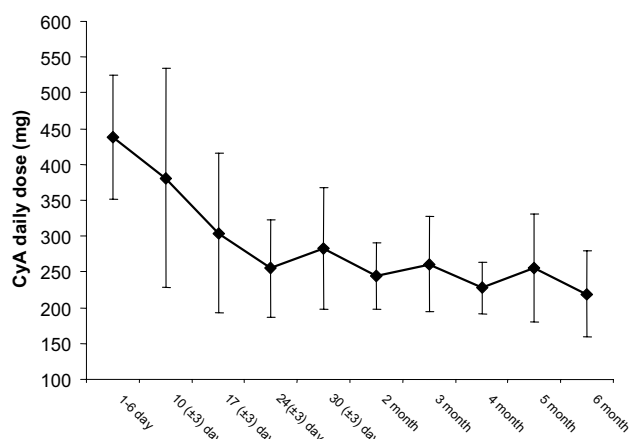


Fig. 1. Mean \pm SD cyclosporine daily dose following the administration of Equoral for 10 renal transplant recipients studied over the 6-month posttransplant period.

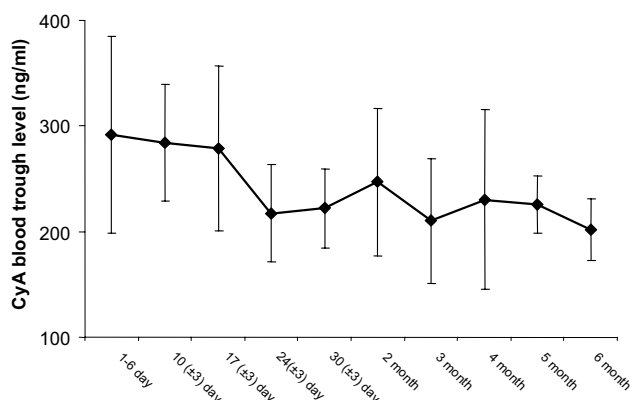


Fig. 2. Mean \pm SD cyclosporine blood trough level following the dose of Equoral for 10 renal transplant recipients studied over the 6-month posttransplant period.

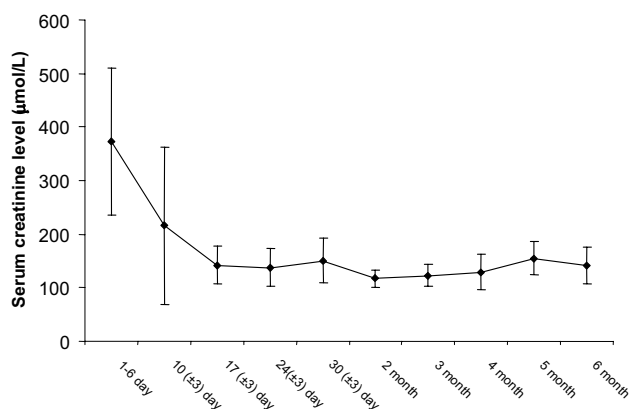


Fig. 3. Mean \pm SD serum creatinine level following the dose of Equoral for 10 renal transplant recipients studied over the 6-month posttransplant period.

to hemodialysis. Cyclosporine levels were measured using a radioimmunoassay (RIA) technique with a monoclonal antibody.

RESULTS

Ten patients were enrolled in the study and followed for 6 months. Number, age and sex distribution are listed in Table 1. The causes of end-stage renal disease before transplantation were especially glomerulonephritis and tubulointerstitial nephritis. Two patients were diabetics; no patients had active hepatitis B or virus C. All ten patients received renal transplants from a cadaver donor.

The administered doses and achieved levels were appropriate (Fig. 1 and 2). The mean maintained daily dose of Equoral® was 345.2 ± 63 mg/day. The mean serum creatinine levels were gradually decreased (Fig. 3). Two acute rejection episodes (20%) proven by biopsy were recovered; they were reversible on high-dose methylprednisolone. Six months patient as well as renal graft survival rate was 100%. The development of the graft function was immediate after transplantation. Over the 6-month posttransplant period, the function of the graft was great and stable.

No specific adverse events were observed in patients treated by Equoral®; the majority of them were those commonly reported with the use of cyclosporine. The adverse events resolved with reduction of the cyclosporine dose, thus readjustment of Equoral® dosage was performed in some cases. Leucopenia was observed in one of ten patients (10%). The hematologic side effect was mild and reversible after cyclosporine reduction. Evaluation of laboratory parameters, vital signs, and physical findings did not demonstrate clinically significant values of these parameters. Some patients (2/10) experienced a mild elevation of liver enzymes; however, these patients responded to reduction of Equoral® doses. No malignancy or lymphoproliferative disease and serious infections were observed. Equoral® treatment demonstrated an acceptable safety profile with maintenance of adequate renal function.

DISCUSSION AND CONCLUSION

The refinement of the immunosuppressive protocols including Equoral® as a representative of calcineurin inhibitors has produced good results regarding the preven-

tion of acute rejection and patient and graft survival after renal transplantation.

Equoral® was well tolerated. No death occurred during the study. The adverse events experienced by subjects were generally mild in nature. Two acute rejection episodes proven by biopsy were occurred during the study and they were reversible on high-dose methylprednisolone. There were no clinically significant differences in adverse events and laboratory values over the 6-month posttransplant period. With the exception of mild hepatotoxicity (demonstrated by an elevation of liver enzymes) and hypertension, there were no reports of other frequently cyclosporine-related adverse events, such as hirsutism, tremor, gastrointestinal disturbance or renal dysfunction (indicated by increased creatinine levels). No serious adverse event was reported in patients treated by Equoral®. There was no apparent effect of the presence of diabetes on the efficacy and safety of Equoral.

Analysis of our first experiences with Equoral®, a generic formulation of cyclosporine for Neoral®, provide clinically relevant evidence of the efficacy and safety profile of this product as part of a triple-drug immunosuppressive regimen in treatment *de novo* adult renal recipients.

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