LETTER TO THE EDITOR

Do we have the same clinical results with Neoral® and Equoral® treatment in kidney transplant recipients? A pilot study

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Cyclosporine (CsA) is characterized by a narrow therapeutic index, significant side effects, and major efforts have been devoted to individualize CsA dosing based on pharmacokinetic parameters, to minimize the toxicity and improve the risk-to-benefit ratio [1]. One of the challenges in CsA management is the poor variable and unpredictable absorption associated with a great intra- and inter-patient variability with a higher risk of acute and chronic rejection incidence, and eventually health care costs [2,3]. Thus, the variable oral CsA bioavailability represents a biopharmaceutical risk factor and deserves particular attention when new formulations are used. The new microemulsion CsA formulation, Neoral® (Novartis, Basel, Switzerland), has been associated with a more reproducible absorption and a better patient outcome compared with the old formulation Sandimmune® (Novartis, Basel, Switzerland). Recently, several generic CsA formulations have been tested as bioequivalent to Neoral®. Bioequivalence tests have been performed in selected groups of young, healthy male volunteers usually in single dose studies, and then extended to completely different population, such as transplant recipients. A growing body of evidence shows that CsA pharmacokinetics in healthy subjects is different from that of transplant patients, treated chronically with CsA. Then, it appears that such a treatment could be detrimental, exposing patients to increased risk of graft function deterioration and graft loss [4]. The incidence of biopsy proven acute rejections at 6 months in *de novo* adult kidney transplant recipients was found significantly higher in patients who received Gengraf® (Abbott) compared with those who received Neoral® [5]. On the other hand, a few studies in stable [6–8] and the only one in *de novo* kidney transplant recipients [9] showed that Equoral® (Ivax, Opava, Czech Republic) could be used as an alternative treatment to Neoral®. Thus, more research and more accurate bioequivalence tests are required to address the unanswered problems dealing with the generic CsA formulations. We compared the pharmacological properties and the outcome at 6 months of treatment with Neoral® versus Equoral® (Ivax) in *de novo* kidney transplant recipients at our transplant unit.

Since the beginning of the year 2006, Equoral® has become available on our market. Hence, in our pilot study, we retrospectively evaluated 16 living related (LR) kidney transplant recipients in the year 2003 (Neoral group) and 15 LR patients transplanted during the year 2006 (Equoral group). All patients received an induction therapy with methylprednisolone (2×500 mg – at the day before and at the operation) and Daclizumab (Zenapax®, Roche, Basel, Switzerland) in five doses. The maintaining triple immunosuppression consisted of: prednisolone, Cyclosporine A (dose adjustment according to the C2 levels) and mycophenolate mofetil (Cellcept®). The database consisted of the average dose of CyA during the first month and up to the sixth month after transplantation and C2 cyclosporine levels from the patients' records. Graft function was followed as a surrogate of the serum creatinine levels at 1 and 6 months after transplantation. The number and treatment of acute rejections (AR) (clinically or biopsy proven) were obtained from the patients' flow charts. A pulse corticosteroids was administered whenever an increase in serum creatinine >20% or decrease in urine output for two consecutive days was observed.

The clinical and biochemical data for analysis were obtained at the time of transplantation as well as at 1 and 6 months after transplantation. Results are expressed as mean values ± SD. An unpaired two-tailed Student t test was used to examine differences in mean values between the groups. Chi square analysis was used to compare the categorical variables. A P-value < 0.05 was assumed significant. The statistical program used was SPSS for windows, release 13 (SPSS, Chicago, IL, USA).

The groups were matched for the demography of mean age, gender and body weight for the Neoral and Equoral group, respectively (Table 1). None of the patients had diabetes, or active hepatitis B or C. The average dose of Neoral® tended to be lower (borderline of significance) up to the first and was significantly lower up to the sixth month in comparison with the Equoral® treatment. The

Table 1. Patient demographics and transplant clinical data.

	Neoral (mean)	Equoral (mean)	*P*-value
n	16	15	
Age (years)	38.6 ± 5.1	39.6 ± 7.6	n.s.
Male gender (%)	9 (56)	11 (73)	n.s.
CyA dose (up to 1 month) (ng/ml)	192.2 ± 55.8	222.3 ± 73.5	0.06
CyA dose (up to 6 months) (ng/ml)	147.8 ± 29.9	191.7 ± 4.1	0.001
C2 (up to 1 month) (ng/ml)	753.5 ± 131.2	639.1 ± 113.1	0.09
C2 (up to 6 months) (ng/ml)	793.2 ± 139.8	597.7 ± 93.4	0.001
Body weight (BW) (kg)	65.5 ± 9.7	70.0 ± 11.4	n.s.
CyA/BW dose (up to 1 month)	2.99 ± 0.94	3.19 ± 1.04	n.s.
CyA/BW dose (up to 6 months)	2.30 ± 0.54	2.76 ± 0.72	0.001
SCr at 1 month (μmol/l)	101.6 ± 34.9	132.3 ± 52.4	0.001
SCr at 6 months (μmol/l)	127.5 ± 43.5	155.5 ± 68.6	<0.05
Acute rej. (AR) up to 6 months (%)	4 (25)	9 (60)	<0.05
AR treatment (MP = gr)	0.84 ± 0.34	1.73 ± 0.64	<0.05
AR treatment (ATG = *n*)	0	2	

CyA, cyclosporine A; C2, cyclosporinemia at 2 h (C2 monitoring); BW, body weight; CyA/BW, cyclosporine dose per kg body weight; SCr, serum creatinine; AR, acute rejection; MP, methyl prednisolone; ATG, anti thymocite globulin.

same observation was found as for the mean C2 levels assessed up to the first and sixth month. When analysed according to the patient's body weight, although lower, the dose of Neoral® didn't reach statistical significance at first month of treatment. However, patients in the Equoral group have received significantly higher dose up to the 6 months of treatment ($P < 0.001$). Serum creatinine levels at 1 and 6 months were significantly lower in the Neoral group. The number of ARs in the Equoral group was significantly higher (9 vs. 4) compared with the Neoral group and significantly higher dose of Methyl Prednisolone therapy was administered (1.73 ± 0.64 vs. 0.84 ± 0.34 gr), respectively. In addition, two patients in the Equoral group received a rescue therapy with antithymocyte globulin (ATG – Fresenius) in a dose of 125 and 650 mg.

Both drugs were well tolerated and no major adverse events occurred during the study period. Regardless of the substantial induction therapy, a significantly higher number of clinically and histologically proven AR was observed in the Equoral® group, which might be related to the significantly lower C2 levels compared with the Neoral® group. In addition, these patients had received significantly higher dose of Equoral®, methyl prednisolon and polyclonal antibodies as a rescue therapy in two cases. As final result, the serum creatinine was significantly higher in the Equoral® group.

To the best of our knowledge, similar studies in kidney transplant patients on Equoral® are scanty and questions may be raised about their design [6–9]. Most of them are dealing with the pharmacokinetic and bioequivalence in stable transplant recipients [6–8]. The limitations of the sole study in *de novo* cadaveric kidney transplant recipients are the small cohort of 10 patients and its uncontrolled design (no controls on Neoral®) [9]. In contrast to our results, Zadrazil *et al.* [9] reported only two (20%) AR episodes for the first 6 months after transplantation. This substantially lower number of AR episodes could be explained by the fact that the cohort was much older (51.6 ± 10.9 years), and the treatment dose of Equoral® was substantially higher at one (≈275 mg/day) and 6 months (≈225 mg/day) after transplantation compared with our patients treated with Equoral®.

Although the use of generic drugs in clinical practice will help in increasing the access to essential medicine, particularly in emerging countries, they should be evaluated not only in chronically treated, but also in *de novo* transplant recipients to confirm their clinical bioequivalence. Besides exposing patients to the increased and unacceptable risk of graft function deterioration and graft loss as compared to the traditional Neoral® formulation, the apparently lower cost of the generic formulations would be overweighed by the additional costs of further, unscheduled interventions and rescue therapy required.

The incidence of ARs up to 6 months after kidney transplantation in our pilot study was found significantly lower in the patients treated with Neoral®. The dose of Equoral® was significantly higher and the C2 levels significantly lower compared with the treatment with Neoral®. The outcome at six months after transplantation as measured by the serum creatinine levels showed better graft function in kidney transplant recipients treated with Neoral®. Therefore, converting patients from Neoral® to the new generic formulations should be very careful, as it might expose patients to an increased risk of graft function deterioration and graft loss. To determine more

accurately the treatment with Equoral® on the clinical outcome in *de novo* kidney transplant recipients, a large-scale randomized controlled trial would be desirable.

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