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Interchangeability of ciclosporin formulations in stable adult renal transplant recipients: comparison of Equoral and Neoral capsules in an international, multicenter, randomized, open-label trial

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The cost of immunosuppression following transplantation can be reduced by using generic ciclosporin (for example, Equoral) rather than innovator ciclosporin drugs such as Neoral. Thus, this study aims to evaluate the interchangeability, safety, and tolerability of Equoral, a generic ciclosporin, with Neoral in stable adult renal transplant recipients. This was a multicenter, randomized, open-label, parallel-group clinical trial in stable renal transplant patients, comparing 6 months of treatment with Equoral with the same treatment period on Neoral. The primary end point was the between-treatment comparison of the total daily ciclosporin dose at the end of the study. A total of 99 patients were enrolled and constituted the full analysis/safety population, and 78 patients forming the per-protocol population were assessed for efficacy. Equoral was found to be equivalent to Neoral with regard to the primary end point of daily dose at the end of the study. This was supported by comparable serum ciclosporin levels at the end of the study. There were no renal transplant rejection incidents, but there was one death (in the Neoral group). Drug tolerability and incidence of adverse events were comparable between the treatment groups. In conclusion, Equoral and Neoral are interchangeable in stable renal transplant patients, and both drugs are associated with a similar safety and tolerability profile.

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Rising health-care costs: a worldwide problem

Health-care costs around the world continue to rise, and a major proportion of these costs is accounted for by drug therapy. One way in which the overall cost of health care can be reduced is to replace original, innovator drugs with generic versions when these are available. Provided that the generic version has been shown to be noninferior or bioequivalent to the innovator drug, an interchange can be an effective cost-saving strategy. This is illustrated by trends in drug use and cost in which the proportion of generic drugs dispensed continues to rise worldwide. For example, approximately two-thirds of all dispensed drugs in the United States are generic products, but these generics account for only 16% of the total US spending on drug therapy.[1]

In the field of organ transplantation, it is notable that a small proportion (15–25%) of total medical expenditure is due to drug costs in the first year of transplantation, but that proportion can increase up to 90% of medical costs in subsequent years.[2] Thus, the use of generic drugs such as ciclosporin for long-term therapy in transplant patients can allow very substantial long-term reductions in health-care cost for this group of patients.[3,4] Another reason for using generic ciclosporin rather than a nonciclosporin innovator immunosuppressant is that calcineurin inhibitors such as ciclosporin or tacrolimus remain the proven standard of care as a part of immunosuppressive regimens, despite the introduction of newer immunosuppressant drugs.

In the case of ciclosporin, a microemulsion formulation (Neoral) has consolidated ciclosporin's position as the mainstay of immunosuppressive therapy in all types of solid organ transplantation.[4–6] Neoral superseded an older oil-based oral formulation of ciclosporin (Sandimmun) associated with widely varying bioavailability and pharmacokinetics. All generic forms of ciclosporin need to show bioequivalence to a well-established form of an innovator drug such as Neoral.[7] This has been shown for a patented soft gelatin capsule formulation of ciclosporin (Equoral), which has been developed by IVAX Pharmaceuticals (Miami, FL, USA; now part of TEVA Group) and approved by regulatory authorities.[8] The bioequivalence of Equoral and Neoral

capsules was proven after single-dose comparative studies of both formulations in healthy volunteers,[9] and in addition, steady-state pharmacokinetic studies in which stable adult renal transplant patients switched from Neoral to Equoral demonstrated comparable pharmacokinetics for the two ciclosporin formulations.[8,10,11] Moreover, a small, 6-month study in *de novo* renal transplant patients has shown clinical equivalence, with patient and allograft survival rates of 100%.[12] The new study reported here (EQUART) investigated the clinical equivalence of Neoral to Equoral in stable renal transplant patients, and constitutes the largest clinical trial of generic ciclosporin to date. The primary objective of this study was to evaluate the interchangeability of Equoral capsules and Neoral capsules in stable adult renal transplant recipients. The secondary objectives were to compare the efficacy, safety, and tolerability of these two ciclosporin formulations.

RESULTS

Patient disposition

A total of 99 patients were enrolled. As they all gave their informed consent, were randomized to a treatment group, and provided post-baseline efficacy data, the full analysis and safety populations thus consisted of 99 patients, 68 (68.7%) of whom were male and 31 (31.3%) were female. All 99 patients were Caucasian, their average age was 42.3 years and the overall mean time since renal transplant was 3.85 years. The baseline demographic characteristics for the full-analysis/safety population, categorized by trial drug, are shown in Table 1. All patients were on ciclosporin, with a similar proportion of patients in each group taking other immunosuppressive agents – mycophenolate mofetil and azathioprine (Table 2).

A total of 21 (21.2%) patients were excluded from the per-protocol analysis population, owing to protocol deviations: 7 (14.9%) from the Equoral group and 14 (26.9%) from the Neoral group. The most common reason for exclusion from the full-analysis population was premature withdrawal from the trial (eight patients; 8.1%), followed by noncompliance with treatment regimen (seven patients; 7.1%) and use of prohibited medications (six patients; 6.1%).

Efficacy

Primary efficacy evaluation (the between-treatment comparisons of the total daily dose) was performed for the per-protocol population ($n = 78$), as shown in Table 3. Although the mean total daily dose of Neoral at baseline and at subsequent trial visits was slightly higher than that of Equoral (Figure 1), equivalence between the two treatments was demonstrated: a between-treatment difference of 2.86 mg (95% confidence interval of 5.08–10.8 mg) at day 180, falling within the prespecified equivalence margin of ± 25 mg (Table 3). Similar results were obtained for the full-analysis set at days 30, 60, 90, and 180 for Neoral and Equoral, and the between-treatment difference at 180 days (3.91 mg; 95% confidence interval: 3.26–11.09 mg) was within the prespecified equivalence margin of ± 25 mg, again demonstrating treatment equivalence.

Mean ciclosporin trough (C0) levels for the per-protocol and full-analysis populations were well matched between the Neoral and Equoral treatment groups at baseline and at the end of the study. Figure 2 shows C0 levels throughout the study, and also shows that mean ciclosporin C0 levels were similar for each treatment group at each trial visit. Treatment equivalence was demonstrated, as the 95% confidence intervals for Equoral (9.58–26.09 ng/ml) were within the prespecified equivalence margin of ± 20% of the adjusted mean value of 130.48 ng/ml (± 26.10 ng/ml) of Neoral C0 concentration at 180 days. Analysis of ciclosporin C0 levels for the full-analysis set also showed treatment equivalence (results not shown).

Mean ciclosporin levels at 2 h after administration of ciclosporin drug treatment (C2 values) were well matched between the Neoral and Equoral treatment groups at baseline and throughout the study, for both the per-protocol and full-analysis populations (Figure 3). Primary analysis for this parameter was performed on the full-analysis set, which showed equivalence at the end of the trial. Treatment equivalence was demonstrated as the 95% confidence intervals for Equoral (−67.48 and 82.35 ng/ml) were within the prespecified equivalence margin of ± 20% of the adjusted mean value of 669.13 ng/ml (± 133.83 ng/ml) of Neoral C2 concentration at 180 days.

There were no renal transplant rejection episodes during the trial, but there was one death during the study in the

Table 2 | Pre-trial immunosuppressive medication continued after randomization for the full-analysis population (*n*=99)

Immunosuppression	Neoral (*n*=52)	Equoral (*n*=47)	Total (*n*=99)
Ciclosporin	52 (100%)	47 (100%)	99 (100%)
Mycophenolate mofetil	30 (57.7%)	30 (63.8%)	60 (60.6%)
Azathioprine	20 (38.5%)	16 (34.0%)	36 (36.4%)
Corticosteroids	47 (90.4%)	40 (85.1%)	87 (87.9%)

Table 1 | Baseline demographic characteristics for the full-analysis set (*n*=99). Data are presented as number (percentage) unless otherwise specified

Characteristic	Neoral (*n*=52)	Equoral (*n*=47)	*P*-value
Sex, male	37 (71.2%)	31 (66.0%)	0.58*
Mean age, years	43.4 years (s.d. 11.6; range 23–67 years)	41.1 years (s.d. 12.5; range 19–68 years)	0.18
Mean weight, kg	77.4 kg (s.d. 17.6; range 45.0–125.0 kg)	77.0 kg (s.d. 13.8; range 43.0–118.5 kg)	0.45
Diabetics	3 (5.8%)	4 (8.5%)	0.60*
Time to transplant, years	4.2 (s.d. 2.6; range 1.0–2.2 years)	3.5 (s.d. 2.6; range 1.0–9.9 years)	

*χ^2.

Table 3 | Between-treatment analysis for the per-protocol population (*n*=78) (primary efficacy variable is the between-treatment difference at 180 days)

Duration of treatment (days)	Adjusted mean		Treatment difference	95% CI (treatment difference)	
	Neoral (*n*=38)	Equoral (*n*=40)	Equoral–Neoral	Lower limit	Upper limit
30	211.50	202.76	–8.73	–16.34	–1.13
60	208.97	205.41	–3.56	–11.75	4.64
90	205.89	209.14	3.25	–4.22	10.71
180	205.64	208.50	2.86	–5.08	10.80

Abbreviation: CI, confidence interval.
All estimates were obtained using analysis of covariance adjusting for baseline and center.

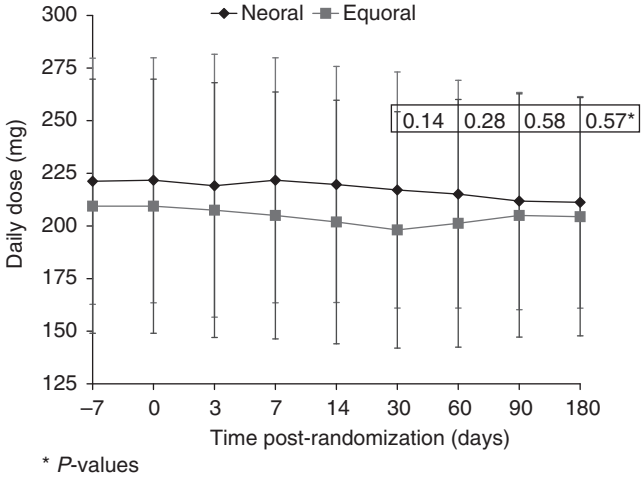

Figure 1 | Efficacy results. Mean daily dose of ciclosporin (per-protocol population; $n = 78$).

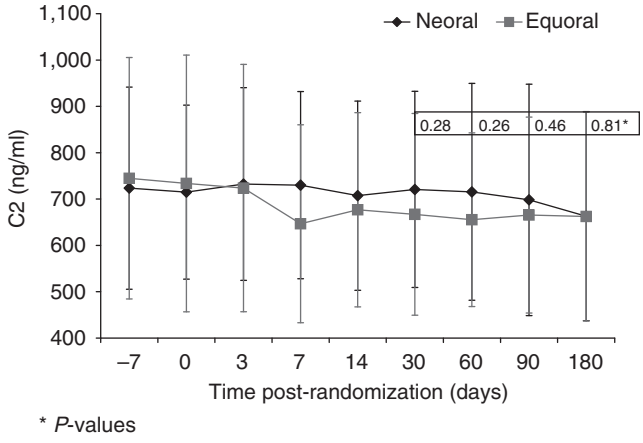

Figure 3 | Efficacy results. Mean ciclosporin levels 2 h after administration of ciclosporin (C2) (per-protocol population; $n = 78$).

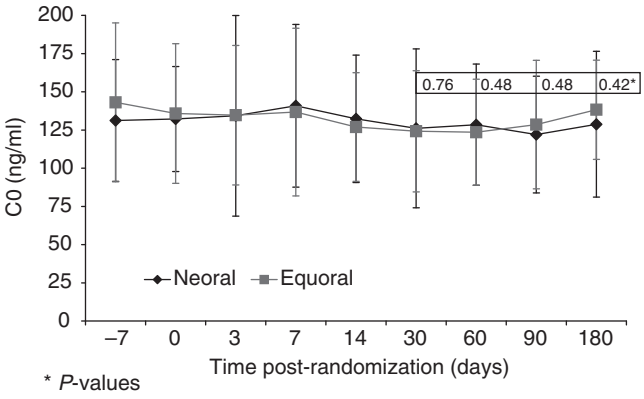

Figure 2 | Efficacy results. Mean trough ciclosporin levels (C0) (per-protocol population; $n = 78$).

Neoral group (owing to cancer of the tongue) in the full-analysis set (there were no other deaths in the per-protocol group or in any patients administered Equoral).

Safety

There were generally no notable differences between the treatment groups in treatment-emergent adverse events, whether according to system organ class or preferred term (Table 4), with the exception of vascular disorders (9.6% in the Neoral group vs 2.1% in the Equoral group). Metabolism and nutrition disorders were the most common system organ class (reported in 17 (17.2%) patients overall), followed by infections and infestations (in 14 (14.1%)). Hyperuricemia (8.1% overall) was the most commonly reported adverse event. The incidence of serious adverse events was similar in the Equoral (6.4%) and Neoral (7.7%) treatment groups. One serious adverse event of cerebral infarction was considered by the investigator to have a possible relationship to Equoral, and events of bronchopneumonia and tongue cancer to have a possible relationship to Neoral. All other treatment-emergent serious adverse events had no relationship to either treatment.

Hematology results, clinical chemistry, vital signs, and physical examinations did not reveal any clinically relevant abnormalities. Moreover, there were no statistically significant changes in red and white blood counts, renal function (creatinine, urea, and uric acid levels), urine protein excretion, serum electrolytes (for example: sodium, potassium, magnesium, calcium, and inorganic phosphorous), liver function tests, serum amylase, total protein, albumin, blood glucose, total cholesterol, or triglyceride levels.

DISCUSSION AND CONCLUSIONS

This study was designed to evaluate the interchangeability of Equoral and Neoral capsules in stable adult renal transplant recipients. The results from this multicenter, randomized, open-label, parallel-group clinical trial indeed showed that

Table 4 | The most common treatment-emergent adverse events (treatment-emergent adverse events reported by less than 3% of patients are not shown)

	Neoral (*n*=52)	Equoral (*n*=47)	Total (*n*=99)
Patients with at least 1 AE	24 (46.2%)	23 (48.9%)	47 (47.5%)
Metabolism and nutrition disorders	8 (15.4%)	9 (19.1%)	17 (17.2%)
Hyperuricemia	4 (7.7%)	4 (8.5%)	8 (8.1%)
Dyslipidemia	2 (3.8%)	1 (2.1%)	3 (3.0%)
Hypercholesterolemia	0 (0.0%)	3 (6.4%)	3 (3.0%)
Hyperlipidemia NOS	2 (3.8%)	1 (2.1%)	3 (3.0%)
Hypertriglyceridemia	2 (3.8%)	1 (2.1%)	3 (3.0%)
Infections and infestations	7 (13.5%)	7 (14.9%)	14 (14.1%)
Urinary tract infection NOS	2 (3.8%)	1 (2.1%)	3 (3.0%)
Gastrointestinal disorders	4 (7.7%)	4 (8.5%)	8 (8.1%)
Gingival hyperplasia	3 (5.8%)	1 (2.1%)	4 (4.0%)
Investigations	3 (5.8%)	3 (6.4%)	6 (6.1%)
Blood creatinine increased	2 (3.8%)	2 (4.3%)	4 (4.0%)
Vascular disorders	5 (9.6%)	1 (2.1%)	6 (6.1%)
Hypertension aggravated	4 (7.7%)	0 (0.0%)	4 (4.0%)
Respiratory, thoracic, and mediastinal disorders	2 (3.8%)	1 (2.1%)	3 (3.0)

Abbreviations: AE, adverse event; NOS, not otherwise specified.

these drugs are interchangeable. The primary interchangeability analysis compared the daily dose of both versions of ciclosporin, and showed treatment equivalence at the end of the study (day 180) in the per-protocol population. Moreover, the daily dose was similar for Equoral and Neoral throughout the study, and treatment equivalence was also demonstrated within the larger full-analysis population at the end of the study. Treatment equivalence was also shown by comparing C0 and C2 levels at the end of the study, and these also support the conclusion that Equoral and Neoral are interchangeable in stable renal transplant patients.

This study included a sizeable population of patients ($n = 99$), although this was somewhat smaller than the planned recruitment of 120 stable renal transplant patients. Nevertheless, the present study extends the results of previous studies which were either conducted in healthy volunteers and compared Equoral and Neoral,[9] or were short-term Equoral/Neoral switching studies in renal transplant patients,[8,10] and a longer term (6 month) noncomparative study in small numbers of *de novo* renal transplant recipients ($n = 10$).[12] There were no rejection episodes reported in either treatment group during the trial, demonstrating the excellent clinical condition of patients under both treatments. This is supported by the good safety and tolerability profile of both drugs, which were associated with a similar incidence of treatment-emergent adverse events.

Although Equoral has been approved in many countries, and has been proven to be bioequivalent to and switchable with Neoral, some authors have raised questions with regard to the use of bioequivalent generic ciclosporin in all groups of patients.[13,14] This study should help to address such concerns in stable renal transplant patients, owing to the randomized, comparative trial design, and sizeable number of study participants.

MATERIALS AND METHODS

Study design and patients

This was a multicenter, randomized, open-label, parallel-group clinical trial designed primarily to evaluate the interchangeability of Equoral and Neoral capsules in stable adult renal transplant recipients. It consisted of a 6-month treatment period with either Equoral or Neoral. The protocol was conducted according to the Declaration of Helsinki principles (1964) and its subsequent amendments and revisions, as well as according to Good Clinical Practice guidelines, and was approved by local independent ethics committees. Patients who gave their written, informed consent were recruited from four centers in the Czech Republic, two centers in Poland, and one location each in Romania, Latvia, and Slovakia. Ciclosporin plasma analyses for all sites were performed at a central laboratory.

Patients were invited to participate if they were aged between 18 and 70 years and had had their first renal transplant between 1 and 10 years before randomization from either a cadaveric or living donor. Additional inclusion criteria included no rejection episodes in the previous 6 months; no liver dysfunction 6 months before trial entry; stable serum creatinine levels for 3 months; no history of alcohol or drug abuse or signs of alcohol-induced organ damage; no history of a malignancy or significant infection; no significant blood pressure changes with or without the aid of antihypertensive medications; with patients being maintained on ciclosporin ($\leqslant 8$ mg/kg) as part of a double or triple combination regime with prednisone and/or azathioprine and/or mycophenolate mofetil, and doses of all these medications having been stable for the 2 weeks before entering the trial, with the last three ciclosporin levels measured before entering the trial having been with an acceptable range without the need for dose adjustment for the last three C0 and C2 values (where C0 is the ciclosporin concentration just before administration of the next dose and C2 is the concentration 2 h after drug administration), with patients able to communicate freely with the study investigators and to comply with study procedures.

Medication

C0 ciclosporin values for each patient were determined and samples taken for hematology, biochemistry, and urine chemistry to check that patients were stable and that there were no changes in patients' laboratory values from prescreening. After determining the stability of the patient, patients were randomized in a 1:1 ratio to receive either Equoral or Neoral for 6 months of treatment with twice-daily oral doses within the dose range of 2–6 mg/kg. Patients randomized to Equoral (that is, swapping from Neoral to Equoral) received a milligram-for-milligram equivalent ciclosporin dose. Ciclosporin doses were adjusted to maintain ciclosporin C0 levels at 75–200 ng/ml and to ensure adequate graft function.

Monitoring, assessments, end points, and analyses

During the treatment phase, visits were performed on day 0 (randomization), and on days 3, 7, 14, 30, 60, 90, and 180 (end of treatment). The primary efficacy variable was the total daily dose (mg) of Equoral or Neoral in patients on days 30, 60, 90, and 180. The assessment on day 180 was considered as the primary end point. Secondary interchangeability end points included ciclosporin C0 and C2 levels on days 30, 60, 90, and 180, and the incidence of rejection episodes and incidence of deaths. Between-treatment comparisons of the daily dose at days 30, 60, 90, and 180 were performed using analysis of covariance, adjusting for baseline daily dose and center, with similar analyses performed for the secondary end points of C0 and C2 levels (with C0 and C2 as covariates in

place of baseline daily dose). Safety was assessed by performing physical examinations and monitoring adverse events, vital signs, and laboratory assessments.

Three populations were defined. The full-analysis set followed intent-to-treat principles in that this population consisted of all patients who provided post-baseline efficacy data, whereas the per-protocol population comprised all full-analysis-set patients, excluding those who incurred a major protocol violation. The safety set consisted of all randomized patients who received at least one dose of a trial drug. The primary analyses of total daily dose and ciclosporin levels were based on the per-protocol population, with secondary analyses of these end points based on the full-analysis set. The primary analyses for all other end points were based on the full-analysis set, with secondary analyses of these end points performed on the per-protocol set.

DISCLOSURE

SV received consulting fees from Wyeth and Bristol and has received lecture fees from TEVA, Novartis, and Astellas. MF is an employee of Teva Pharmaceuticals.

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