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UK multicentre study to assess the safety and tolerability of Neoral in stable renal transplant patients

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Abstract The safety and tolerability of transferring maintained renal transplant patients from Sandimmun to Neoral is being assessed in a multicentre, open-label, single-arm study. A total of 250 patients has been enrolled and results are available from 75 patients up to 12 months post-transfer. A slight trend to higher mean cyclosporin trough levels was seen in this cohort, but trough levels were unchanged in the sub-group receiving ≥ 1 dose changes. The mean dose fell by 13 %. Creatinine levels showed a slight overall upward trend. Blood pressure and uric acid were unchanged and adverse events were typical of those seen with Sandimmun. Neoral was well-tolerated. Data from the full cohort of 250 patients up to 3 months post-transfer support these findings. These results indicate that transfer from Sandimmun to Neoral is safe and well-tolerated and provides appropriate immunosuppression at a lower average dose than Sandimmun. The Neoral dose should be adjusted promptly, as required, to maintain the target trough level.

Key words Cyclosporin · Neoral · Immunosuppression

Introduction

Since its introduction in the early 1980s, cyclosporin has become the cornerstone of rejection prophylaxis in solid organ transplantation. It has improved survival rates significantly: for example, survival of renal allografts has increased from around 65 % 1 year after transplantation in the pre-cyclosporin era to up to 90 % now [3].

Cyclosporin is, however, a highly lipophilic molecule. The conventional formulation of cyclosporin, Sandimmun, forms a coarse emulsion in water which rapidly precipitates, leading to poor and unpredictable absorption from the gut. In contrast, Neoral forms a very fine emulsion of tiny droplets less than 100 nm in diameter. As a result, Neoral provides a significantly more predictable, consistent and rapid absorption of cyclosporin from the upper gastrointestinal tract than does Sandimmun [1].

Pharmacokinetic comparisons in renal patients have demonstrated that the improved absorption of cyclosporin using Neoral provides a number of benefits compared to Sandimmun [2]:

1. More predictable blood levels of cyclosporin.
2. Reduction in intrapatient pharmacokinetic variability.
3. An increase in area under the curve (AUC) of 29 %.
4. Trough cyclosporin levels become a more meaningful clinical measurement. Neoral shows a markedly improved correlation between trough levels and drug exposure (correlation coefficient of approximately 0.8 in renal transplant patients given Neoral versus approximately 0.5 with Sandimmun).

A number of international trials have demonstrated that transferring renal transplant patients from the Sandimmun formulation to the Neoral formulation of cyclosporin is both safe and well-tolerated. A multicentre UK trial of 250 stable renal allograft recipients (NEO 001) is further assessing the pharmacokinetic and clinical impact to transfer to the new formulation.

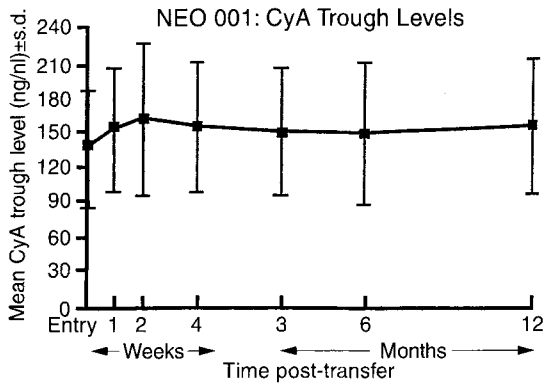

Fig. 1 Cyclosporin *(CyA)* trough levels in 75 maintained renal transplant patients following transfer from Sandimmun to Neoral

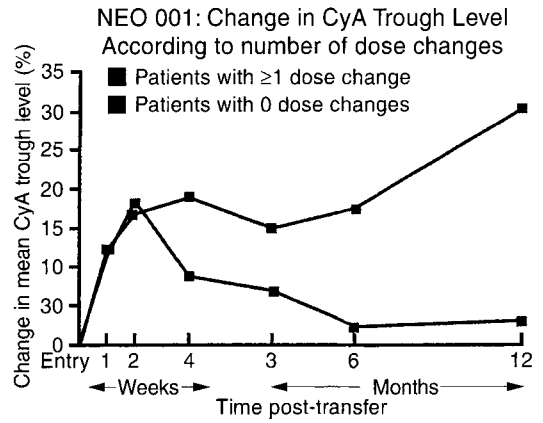

Fig. 2 Cyclosporin trough levels in 75 maintained renal transplant patients following transfer from Sandimmun to Neoral, stratified according to number of dose changes

Materials and methods

Subjects

Two hundred and fifty renal transplant recipients with a mean age of 49.4 years (range 17–80 years) and a median of 2.18 years post-transplant (range 0.3–10.9 years) were recruited at 22 centres. Seventy-seven patients were female, 170 were male. Two hundred and twelve patients (84.8 %) were primary transplants, 25 (10.0 %) were diabetic and 218 (87.2 %) were hypertensive. All patients were are least 6 months post-transplant and had experienced no episodes of rejection in the 3 months prior to entering the study.

Study design

The study was an open-label, single-arm study. Clinical and pharmacokinetic assessments were carried out at entry, 1, 2 and 4 weeks and at 3, 6 and 12 months. At the entry visit, all patients were transferred from Sandimmun to Neoral on a 1:1 dose conversion. Cyclosporin trough levels, dose, serum creatinine, blood pressure, use of antihypertensives, uric acid, presence of infection and adverse effects were recorded at each visit. Tolerability was assessed by the investigator and by the patient. Any change in dose and the reason for the dose change was also recorded.

Results

Data up to 12 months are now available for 75 of the patients enrolled in the study.

Cyclosporin trough levels

In this group of patients there was a slight trend to higher cyclosporin trough levels during the 12 months of the study, from 138.4 ng/ml at entry to 156.4 ng/ml at 12 months (Fig. 1). However, in those patients who had one or more dose changes, trough levels remained approximately unchanged, while those who did not receive a dose alteration showed a mean trough level increase of 30 %, accounting for the overall mean rise (Fig. 2).

Cyclosporin dose

The mean dose was reduced by 13 % over the study period, with 45 out of these 75 patients receiving one or more dose changes. There were 92 dose changes in total, of which 65 were decreases and 27 were increases. During the study period, the majority of dose changes (79 %) were made in response to trough cyclosporin levels.

Renal function

Creatinine levels showed a slight overall upward trend during the study period (151.5 μmol/l at entry to 169 μmol/l at 12 months), in line with the trend to an increase in trough cyclosporin levels resulting from the cohort of patients who did not receive a dose change (Fig. 3).

Adverse events and tolerability

Blood pressure was unchanged and there was no change in the use of antihypertensive medication. Uric acid levels were also unaltered 12 months after transfer to Neoral. Infections and adverse events were typical of those seen with Sandimmun therapy, with no unexpected events occurring.

Both the invesigators and patients reported 'very good' or 'good' tolerability in over 95 % of cases following transfer to Neoral.

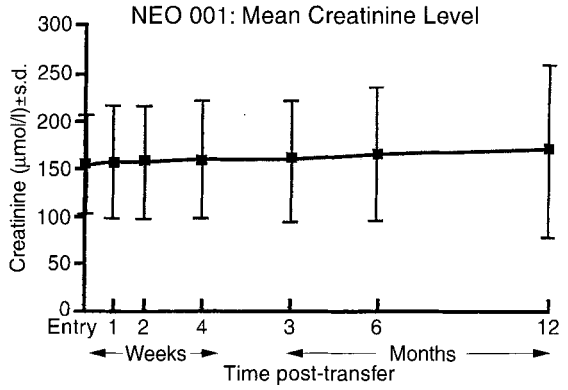

Fig. 3 Serum creatinine levels in 75 maintained renal transplant patients following transfer from Sandimmun to Neoral

Status 3 months after transfer (full cohort)

Data up to 3 months post-transfer are now available from the full study cohort of 250 patients. Trough cyclosporin levels remained largely constant during the first 3 months of the study, from 161 ng/ml at entry to 155 ng/ml at 3 months (a change of 3.6%). In patients who had a dose alteration following transfer to Neoral, mean trough levels fell from 182 ng/ml at entry to 162 ng/ml at 3 months. In the group who had no change in dose following transfer to Neoral, the trough level was 145 ng/ml at entry, rising marginally to 149 ng/ml after 3 months.

The mean creatinine level remained stable during the first 3 months of the study (146 μmol/l at entry compared to 149 μmol/l at 3 months) in this full cohort of 250 patients.

Discussion

These results support the findings of international double-blind trials in which renal transplant patients have been transferred from Sandimmun, the conventional formulation of cyclosporin, to Neoral. The transfer is safe and well-tolerated, with no significant change in the nature, incidence or severity of adverse effects.

Using Sandimmun, trough cyclosporin levels have provided only an imprecise estimate of total drug exposure. In patients receiving Neoral, however, it is clear that trough cyclosporin levels become a meaningful clinical measurement, and the result of this trial highlight that the dose of Neoral should therefore be adjusted promptly, where necessary, on the basis of trough cyclosporin measurements in order to maintain target blood levels.

Finally, these findings also confirm that Neoral can provide appropriate levels of immunosuppression at a lower mean dose than Sandimmun, offering the potential for considerable cost savings. In the clinical setting, a mean dose reduction of around 10% could realistically be expected following transfer to Neoral. Since any new immunosuppressive agent must now be assessed in health economic terms as well as incremental clinical benefit, this fulfils an important criterion for transplant centres evaluating their current immunosuppressive protocols.

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