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E.A. Mueller
J.M. Kovarik
J.B. van Bree
A.E. Lison
K. Kutz

Safety and steady-state pharmacokinetics of a new oral formulation of cyclosporin A in renal transplant patients

E.A. Mueller · J.M. Kovarik
J.B. van Bree · K. Kutz
Departments of Human Pharmacology and
Biopharmaceutics, Sandoz Pharma Ltd.,
CH-4002 Basle, Switzerland

A.E. Lison
Internal Medicine Clinic, Central Hospital,
D-28205 Bremen, Germany

Abstract The steady-state pharmacokinetics of a new oral formulation of cyclosporin A (Sandimmun Neoral, NOF, a microemulsion) was compared with those of the market formulation (Sandimmun, SIM) in stable renal transplant patients. Both formulations were administered as soft gelatin capsules every 12 h with doses adjusted to provide comparable trough concentrations (C^{ss}_{min}). Whole blood samples were obtained over a steady-state dosing interval (τ), and the cyclosporin A level was determined by a specific monoclonal RIA. Both formulations were well tolerated. The mean doses were 139 ± 27 mg (SIM) vs. 120 ± 19 mg (NOF), indicating a milligram dose-conversion factor of approximately 1:1 to yield comparable troughs. NOF exhibited a stronger correlation between AUC^{ss}_{τ} and C^{ss}_{min} ($r^2 = 0.821$) compared with SIM ($r^2 = 0.288$), due in part to less variability in the NOF profiles. Average increases of 39% in C^{ss}_{max} and 15% in AUC^{ss}_{τ} during treatment with NOF were not associated with any safety concerns over the 4-week exposure to Sandimmun Neoral, as evidenced by the absence of changes in blood pressure, hematologic and biochemical parameters (including serum creatinine and blood urea nitrogen, BUN) and ultrasound of the transplanted kidney.

Key words Cyclosporin A
Pharmacokinetics
Renal transplantation
Dosage form

Introduction

Cyclosporin A (CsA) has had a substantial impact on organ transplantation by significantly reducing the rate and severity of rejection episodes [1]. However, studies in several transplant patient populations have indicated that CsA absorption and disposition from the commercially available oral formulation are markedly variable [2], which is of particular concern for a drug such as CsA which has a narrow therapeutic window. It is therefore anticipated that an oral CsA formulation with a more consistent absorption process and lower pharmacokinetic variability would facilitate the management of patients during CsA therapy and would consequently have a beneficial effect on graft survival [3]. With this objective in mind, a microemulsion formulation of CsA was developed.

Patients and methods

Steady-state pharmacokinetic profiles of CsA following the multiple administration of SIM and NOF were compared on four different

occassions in clinically stable renal transplant patients aged 46±15 years (mean ± SD) and weighing 70.6±7.8 kg. At study entry, the time post-transplant range from 6 to 26 months.

Eighteen clinically stable renal transplant patients completed this open label study. Each patient received an individualized twice-daily treatment of SIM followed by a 4-week treatment of NOF and reinstitution of SIM after NOF treatment. Both formulations were administered as soft gelatin capsules every 12 h with doses adjusted to provide comparable trough concentrations. Steady-state pharmacokinetic profiles were assessed under fasting conditions on four occassions: period I, 2 weeks after study start while on SIM; period II, 2 weeks after switching to NOF; period III, after an additional 2 weeks on NOF following dose adjustments designed to atain similar trough concentrations as in period I; period IV, 2 weeks after switching back to SIM at the same dose as in period I. Serial blood samples for pharmacokinetic analysis was obtained over a 12-h dosing interval. Safety was assessed by physical examiniation, vital signs measurements, routine hematologic and biochemical tests, and ultrasound of the transplanted kidney. Whole blood concentrations of CsA were measured by a specific monoclonal radioimmunoassay method with a limit of quantification of 12.5 ng/ml.

Results

Both study drug formulations were well tolerated. The only adverse event reported was flu-like symptoms during period IV in one patient. Ultrasound examination of the transplanted kidney did not reveal any clinically relevant changes in any patient throughout the study. Hemograms, biochemistry profiles, and urinanalysis assessments remained stable over the duration of the study. In particular, NOF had no effects on blood pressure or serum concentrations of urea, uric acid, potassium, and fasting cholesterol and triglycerides. Specifically, at screening, at the end of the 4-week treatment with NOF, and at study completion, the serum creatinine level was 1.6±0.4, 1.4±0.3, and 1.5±0.4 mg/dl.

The concentration-time data could be successfully simultaneously fitted by nonlinear regression analysis employing common disposition parameters for all four steady-state profiles for each patient, indicating that the disposition of CsA is formulation-independent. Pharmacokinetic differences between the formulations were absorption-related. Specifically, the maximum whole blood concentration was higher and the time of its occurrence earlier for NOF than for SIM (Table 1).

The dose of NOF necessary to achieve comparable troughs as in period I on SIM was 120±19 vs. 139±27 mg. This represents a steady-state dose conversion of 0.9 based on the geometric mean of the NOF/SIM dose ratios. The data also indicated that concomitant with this dosage conversion, the following increases occur (based on the geometric mean of the intraindividual NOF/SIM parameter ratios): a 39% increase in $C^{ss}_{max,b}$ and a 15% increase in $AUC^{ss}_{\tau,b}$ as compared with SIM. The relationship between $AUC^{ss}_{\tau,b}$ and $C^{ss}_{min,b}$ was much stronger for NOF ($r^2 = 0.821$) than for SIM ($r^2 = 0.288$). This was due in part to the greater consistency in the concentration-time profiles following NOF administration.

Table 1 Steady-state pharmacokinetic parameters (mean ± SD)

	t_{max} (h)	C^{ss}_{max} (ng/ml)	C^{ss}_{min} (ng/ml)	AUC^{ss}_{τ} (ng·h/ml)	C^{ss}_{av} (ng/ml)
SIM	2.0±0.8	705±242	87±23	2983±732	245±61
NOF	1.6±0.5	960±207	93±13	3356±489	280±41

Discussion

In this concentration-controlled trial, conversion between SIM and NOF was based on titrating the CsA dose to yield comparable steady-state trough concentrations. The data indicate that, for stable renal transplant patients, this can be achieved by maintaining the same CsA dose (1:1 switch) when changing from SIM to NOF. Concomitant with this change-over, $C^{ss}_{max,b}$ and $AUC^{ss}_{\tau,b}$ increased on average by 39% and 15%, respectively, due to absorption-related differences between the formulations. Increases of this magnitude were not associated with tolerability problems or changes in blood pressure or clinical laboratory parameters. Furthermore, they were not detrimental to the transplanted kidney as assessed by ultrasound examination. In this context, the 1-month duration of treatment with NOF requires explanation. Since the most important and frequent adverse events associated with CsA treatment occur generally within the first month of treatment initiation [4, 5], changes in the safety profile of CsA when administered as NOF are likely to have manifested during this study.

Trough concentration monitoring has proved to be a useful adjunct to successful immunosuppression therapy with CsA [6, 7]. Whether it serves as an optimal parameter for guiding dosage adjustment, however, has been questioned because of its inability to reflect systemic exposure adequately in terms of the area under the curve [8]. The results from the present investigation demonstrate that the correlation between CsA trough concentration and the area under the curve is markedly stronger during treatment with NOF than with SIM. It is therefore anticipated that with Sandimmun Neoral trough concentrations will be a more precise predictor of systemic CsA exposure and therefore a more reliable and robust parameter, thereby reducing the risk of over- or underdosing patients, which is critical for drugs with a narrow therapeutic window.

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