



New oral formulation of cyclosporin A (Neoral) pharmacokinetics in allogeneic bone marrow transplant recipients

N Parquet^{1,2}, O Reigneau³, H Humbert³, M Guignard³, P Ribaud¹, G Socié¹, A Devergie¹, H Espérou¹ and E Gluckman¹

¹Bone Marrow Transplant Unit, Hospital Saint Louis, Paris; ²Hematology Hospital Paul Brousse, Villejuif; and ³Novartis France, Rueil Malmaison, France

Summary:

Cyclosporin A (CsA) absorption is variable in bone marrow transplant (BMT) patients compromising the efficacy of graft-versus-host disease prevention. Neoral, a new microemulsion formulation of CsA which has an improved bioavailability, increases intestinal absorption of the drug with less variable pharmacokinetic parameters in non-BMT patients. In order to predict the best dosage of Neoral when patients are switched from i.v. to oral administration we performed a randomised study comparing two oral doses, either the same or twice the last i.v. dose used after BMT. Fourteen adults were randomised around day 25 after BMT. Whole blood CSA concentrations were measured 2 and 12 h after the oral administration of Neoral on days 0, 7 and 14 to determine residual and maximum concentration, and modified whenever necessary to maintain blood level CsA concentration within therapeutic range (150–250 ng/ml). We found that patients who received twice the last i.v. dose had better concentrations than patients from the other group while toxicity was identical in both groups. We conclude that doubling the last i.v. dose during the switch to oral administration of Neoral gives the best therapeutic range concentration and should be recommended for graft-versus-host prevention. *Bone Marrow Transplantation* (2000) 25, 965–968.

Keywords: bone marrow transplantation; cyclosporin A; pharmacokinetics

in pharmacokinetic parameters within and between patients.^{1,2} Several comparative studies in *de novo* transplant patients have shown that the clinical efficacy of Neoral is equivalent to, or even better than Sandimmun with a comparable safety profile.³ The improved bioavailability is of particular benefit in some patients who have severe malabsorption (liver transplant patients, cystic fibrosis, gut graft-versus-host disease), requiring intravenous CsA to reach the therapeutic blood levels in the early post-transplant period. Many studies have shown that it is possible to initiate the microemulsion Neoral immediately post transplant thereby avoiding the intravenous route of administration.

Few data are available on the pharmacokinetics of CsA in marrow transplant recipients.⁴ This is particularly important in this group of patients who very often have problems of intestinal absorption. The aim of our study was to determine the optimal initial dose of oral Neoral after intravenous infusion of CsA in allogeneic bone marrow transplant recipients.

Patients and methods

This was a two arm randomised study to determine the optimal initial dose of Neoral. All participants in the study provided written informed consent. The protocol was approved by the Ethics Committee.

Patient population

Patients were included in the study if they were older than 18 years, had received a first bone marrow transplant from HLA-genotypical or unrelated donor, had been receiving intravenous CsA as graft-versus-host disease (GVHD) prophylaxis, and were able to eat. Patients were excluded if they developed grade II–IV acute GVHD, had received another experimental drug in the 4 weeks before the study, showed evidence of noncontrolled infection, presented renal dysfunction (defined as serum creatinine concentration >200 $\mu\text{mol/l}$) or hepatic dysfunction (defined as serum transaminases level >5 N and/or total bilirubin level >50 $\mu\text{mol/l}$), presented cardiac dysfunction or visceral failure or were not able to cooperate.

Fourteen patients were enrolled in the study. Data were analysed at 6 months after completion of the study. Sex distribution was nine males and five females, aged from 18

In an attempt to improve the bioavailability of oral cyclosporin A (CsA) and to reduce variability in absorption, a new microemulsion formulation of CsA has been developed (Neoral).

Pharmacokinetic studies conducted in healthy volunteers and renal, liver and cardiac transplant recipients have consistently demonstrated that absorption was increased by an average of 30% in the area-under-the-curve and was faster after Neoral than after Sandimmun. This results in an increased bioavailability, a lower dependency on food, bile or pancreatic enzymes and a markedly reduced variability

to 55 years (median 43 years). Seven patients had chronic myelogenous leukaemia (CML), four had acute myeloblastic leukaemia in complete remission, one had aplastic anaemia, one had Hodgkin's lymphoma and one had myelomonocytic leukaemia. The conditioning regimens used for transplantation were those used at our institution during the time period patients were transplanted (either high-dose chemoradiotherapy or high-dose chemotherapy). Protocol for GVHD prophylaxis consisted of CsA and methotrexate days 1 (15 mg/m²), 3, 6, and 11 (10 mg/m²) post BMT for 11 patients, and CD34-positive selection of bone marrow cells and CsA in the three patients who received bone marrow from unrelated donors. CSA was started by continuous i.v. infusion at the dose of 3 mg/kg. The dose was then adjusted according to blood levels and measurement of urea and creatinine. The maximum tolerated dose was used. The source of stem cells was bone marrow in 13 patients and peripheral blood stem cells in one patient. Marrow donors were unrelated in three patients and related in 11 patients. Total number of nucleated marrow cells infused ranged from 0.4 to 9.9 (median 2.2) × 10⁸/kg of recipient body weight in patients who received unmanipulated marrow. The clinical diagnosis of GVHD was confirmed by appropriate biopsies and clinically graded as 0 to IV by the criteria reported for acute GVHD according to the Seattle criteria.^{5,6}

Patients were hospitalised in isolation rooms with laminar airflow. They received antimicrobial prophylaxis with absorbable antibiotics, oral fungal infections prophylaxis with fluconazole and amphotericin B, and *Pneumocystis carinii* prophylaxis with cotrimoxazole. For Herpes virus prophylaxis, patients received acyclovir 250 mg/m²/8 h in related marrow transplants and 350 mg/m²/8 h in unrelated marrow transplants. Leukocyte poor irradiated blood component support was used to maintain a minimum platelet count of 20 × 10⁹/dl and a haemoglobin of 8 g/100 ml.

Study schedule

When patients were able to eat normally, usually around day 25 after BMT, they were randomised to switch from intravenous CsA to oral Neoral at the same dose or at twice the last dose. They were followed for 14 days for clinical and biological parameters. Thereafter, Neoral was given for at least 6 months and then tapered according to the existence of chronic GVHD.

Medication

Fourteen patients received the last dose of intravenous CsA (continuous infusion during 24 h) and the measure of whole-blood concentration was performed just before the switch. Capsules were taken according to individual dosage requirements. The daily dose was taken in two equally divided doses at 12 h intervals. Whenever possible, no nephrotoxic or drugs that interfere with CsA pharmacokinetic were allowed during the study.

Clinical assessments

One day before starting the study, serum CsA concentration (intravenous administration) was determined. On the first

day of treatment with Neoral (day 0) laboratory and clinical variables were measured. Vital signs and laboratory variables (renal and liver function tests) were repeated during outpatient visits at days 3, 7 and 14. CsA in its native form was monitored by measurement of whole-blood concentrations using a specific monoclonal antibody (kit CYCLOTRAC; SP-all blood, INCSTARS, distributed in France by SORIN, Anthony, France) measured 12 h after the oral administration of Neoral on days 0, 3, 7 and 14 to determine the residual concentration, and 2 h after the oral administration on days 0, 7 and 14 to determine the maximal concentration.

During the study, the dose of medication was modified, whenever necessary, to maintain the blood trough CsA level within the therapeutic range as defined by the investigator before the start of the study (150–250 ng/ml) or in response to adverse events.

Safety and tolerability assessments

At every study visit, patients were examined for the presence of adverse events, any clinical relevant laboratory data were recorded for each patient.

Data analysis and statistical methods

Comparisons between both treatment groups were performed by determination of the optimal initial dose of Neoral which allowed reaching quicker residual CsA concentrations within the therapeutic range as defined on day 0, by determination of frequency for dose adjustments in each treatment group and by evaluation of digestive absorption of Neoral. Comparison was performed using χ^2 -test for qualitative variables and using Mann–Whitney for continuous variables. To compare the total exposure to CsA, over a whole day, the individual area under the concentration time curve (AUC (0–12 h)) was calculated according to the formula: $AUC(0-12\text{ h}) = 441.2 + 12.34C_{12} + 2.48C_2$.⁷ Then, the steady-state (C_{ss}) concentration by oral route ($C_{ss} = AUC/12$) was compared to the concentration observed after intravenous administration (C_{iv}).

Results

Eight patients were enrolled in group 1 (same oral and i.v. dose) and six patients in group 2 (twice the last i.v. dose). Neoral treatment duration (in the study) was 12.8 days (12–13) in group 1 and 12.2 days (7–14) in group 2. None of the patients stopped the treatment during the study except one who stopped the treatment for 1 day because of misinterpretation of the prescription.

Pharmacokinetic analysis (Table 1)

In group 1, the steady-state concentration after oral administration was lower than after the intravenous route. The median individual ratio C_{ss}/C_{iv} was 0.75 (range 0.31–1.26) and showed a lower than expected level by oral vs intravenous route. Four out of eight patients presented a decrease of more than 25% of the optimal dose of CsA. In

Table 1 Steady-state cyclosporine blood level after oral and intravenous routes

	Median ng/ml (min-max)	Median ratio Css/Civ
Group 1		
Css	253 (116-348)	
Civ	293 (125-915)	0.75
Group 2		
Css	353 (227-466)	
Civ	273 (120-460)	1.4

Css = steady-state oral concentration; Civ = i.v. concentration.

Table 2 Cyclosporine peak and trough levels (2 h and 12 h after drug intake sampling)

	Patient's group	CsA peak blood level median (ng/ml) (min-max)	CsA trough level Median (ng/ml) (min-max)
Day 0	1	348 (80-1000)	125 (50-1920)
Day 0	2	745 (345-1400)	120 (50-150)
Day 3	1		170 (55-240)
Day 3	2		185 (75-230)
Day 7	1	530 (230-655)	80 (55-240)
Day 7	2	573 (340-1210)	120 (65-430)
Day 14	1	405 (65-580)	100 (30-175)
Day 14	2	605 (315-925)	123 (35-455)

group 2, the steady-state concentration after oral was higher than after the intravenous route. The median individual ratio *Css/Civ* was 1.4 (range 0.85-2.74) and an increased level by oral route as compared to intravenous. One patient only had a slightly reduced level (-15%).

Maintenance of blood CsA levels (Table 2)

There was a trend for a higher proportion of patients in group 2 to be in the therapeutic range compared with group 1. The mean residual CsA concentration 12 h after oral administration was more likely to be in the therapeutic range in group 2 than in group 1.

Clinical laboratory data (Table 3)

No notable increase in serum creatinine value was observed in either group. The mean value remained stable in both

Table 3 Biochemistry. Serum creatinine level

	Patients group	Mean (µmol/l)	Min-Max
Day 0	1	103	71-179
Day 0	2	99.8	85-117
Day 3	1	98.1	70-139
Day 3	2	113.7	87-168.2
Day 7	1	102.3	68-145
Day 7	2	122.8	100-145
Day 14	1	112.5	86-148
Day 14	2	122	94-146

groups. No clinically relevant differences between the treatment groups were observed with respect to other laboratory variables.

Tolerability and safety

No clinically significant changes in vital and biological parameters occurred in either group. No serious adverse events were observed during the study with no clinically significant changes in systolic and diastolic blood pressure level (Table 4).

Discussion

CsA was introduced as an immunosuppressive agent more than 15 years ago.⁸ CsA is used to prevent or treat acute and chronic GVHD after allogeneic BMT; studies have shown that CsA combined with either methotrexate or steroids prevents acute GVHD and that CsA is effective in the treatment of established acute GVHD.⁹⁻¹² CsA absorption has been highly variable in BMT patients and average bioavailability is about 30%, values ranging from 10 to 60%.¹³ Absorption of the drug from the gastrointestinal tract is highly variable, depending on emulsification by bile salts, influenced by bile flow and composition, presence of food and gastrointestinal motility.¹³ Because of this variability in the pharmacokinetic parameters, Neoral, a new microemulsion formulation of CsA gives less variable pharmacokinetic parameters in renal transplant recipients.¹⁴⁻¹⁶ Absorption of Neoral is more rapid and less variable than with Sandimmun (traditional oil-based formulation of CsA).¹⁷ In renal and heart transplantation, the authors converted from the conventional to the microemulsion CsA formulation in a dose ratio of 1 to 1 mg.¹⁴⁻¹⁶ In this study we attempted to determine the dose conversion from intravenous CsA to Neoral in allogeneic BMT recipients.

Our results show that the conversion in a dose ratio of 1 mg Neoral to 1 mg CsA in the switch from intravenous to oral administration leads to an important under exposure for some patients (four patients of the eight in group 1). On the other hand, the conversion in a dose ratio of 1 to 2 allows optimal therapeutic exposure in all patients to be obtained. Indeed, in group 2 only one patient showed a slight under exposure after oral switch, and this under exposure was limited to 15%. However, the dose of Neoral

Table 4 Blood pressure measurement

	Blood pressure level (mm Hg)	Mean	Min	Max
Day 0	Systolic	110	100	135
	Diastolic	73.6	60	90
Day 3	Systolic	115	80	140
	Diastolic	73.5	50	90
Day 7	Systolic	123.8	95	150
	Diastolic	77.5	60	100
Day 14	Systolic	125	110	140
	Diastolic	72.5	60	90

must be regularly monitored and adjusted in the dose ratio 2 to 1 in order to decrease the risk of over exposure in some patients. These results are in line with a study which showed that the switch from i.v. CsA to Neoral at a ratio of 1:3 produced significantly more renal dysfunction than a ratio of 1:1; however, the authors did not test the 1:2 ratio nor the CsA levels.¹⁸

Neoral bioavailability is 30% higher than oral Sandimmun.² The absolute bioavailability (oral vs i.v.) of Sandimmun is 30%,¹³ consequently the absolute bioavailability of Neoral is about 40%. These pharmacokinetic parameters explain why the ratio was the same in the switch from intravenous CsA to Neoral and Sandimmun, because the difference in absorption is not sufficiently increased with Neoral compared to Sandimmun. An increase of 10% of the bioavailability between the two oral CsA formulations would benefit patients, especially those patients who present malabsorption. The CsA-related adverse events (hypertension, tremor, headache, nausea, metabolic disturbances) did not appear different with Neoral with regard to Sandimmun although we did not make any comparison with a control group receiving classic formulation Sandimmun.

In summary, this study shows that the conversion in a ratio of 2 to 1 in the switch from intravenous CsA to oral Neoral is the most effective way to obtain optimal therapeutic concentrations.

References

- Holt DW, Mueller EA, Kovarik JM *et al*. The pharmacokinetics of Sandimmun Neoral: a new oral formulation of cyclosporine. *Transplant Proc* 1994; **26**: 2935–2939.
- Holt DW, Johnson A. Cyclosporine microemulsion. *Biodrugs* 1997; **7**: 175–197.
- Sullivan KM, Shulman HM, Storb R *et al*. Chronic graft-versus-host disease in 52 patients: adverse natural course and successful treatment with combination immunosuppression. *Blood* 1981; **57**: 267–276.
- Cole E, Keown P, Landsberg D *et al*. Safety and tolerability of cyclosporine and cyclosporine microemulsion during 18 months of follow-up in stable renal transplant recipients. *Transplantation* 1988; **65**: 505–510.
- Thomas ED, Storb R, Clift RA *et al*. Bone marrow transplantation. *New Engl J Med* 1975; **292**: 832–843, 895–902.
- Yee GC. Pharmacokinetic and pharmacodynamic studies of cyclosporine in bone marrow transplantation. *Transplant Proc* 1990; **22**: 1327–1330.
- Humbert H. Variabilité de la biodisponibilité de la ciclosporine: avantage de la formulation Néoral. *Thérapie* 1996; **52**: 353–357.
- Atkinson K. Cyclosporin in bone marrow transplantation. *Bone Marrow Transplant* 1987; **1**: 265–270.
- Yee G, McGuire T, Honaker M *et al*. Serum cyclosporin concentration and risk of acute graft-versus-host disease after allogeneic bone marrow transplantation. *New Engl J Med* 1988; **319**: 65–70.
- Calne RY, White DJG, Thiru S *et al*. Cyclosporin A in patients receiving renal allografts from cadaver donors. *Lancet* 1978; **II**: 1323–1327.
- Gratwohl A, Speck B, Wenk M *et al*. Cyclosporine in human bone marrow transplantation. Serum concentration, graft-versus-host disease, and nephrotoxicity. *Transplantation* 1983; **36**: 40–44.
- Feutren G, Wong R, Jin J *et al*. Safety and tolerability of Neoral in transplant recipients. *Transplant Proc* 1996; **4**: 2177–2182.
- Primmitt DRN, Levine M, Kovarik JM *et al*. Cyclosporine monitoring in patients with renal transplants: two- or three-point methods that estimate area under the curve are superior to trough levels in predicting drug exposure. *Therapeutic Drug Monitor* 1998; **20**: 276–283.
- Friman S, Bäckman L. A new microemulsion formulation of cyclosporin. Pharmacokinetic and clinical features. *Clin Pharmacokinetics* 1996; **30**: 181–193.
- Frei UA, Neumayer HH, Buchholz B *et al*. Randomised, double-blind, one-year study of the safety and tolerability of cyclosporine microemulsion compared with conventional cyclosporine in renal transplant patients. *Transplantation* 1998; **65**: 1455–1460.
- Storb R, Deeg H, Whitehead J *et al*. Methotrexate and cyclosporin compared with cyclosporin alone for prophylaxis of acute graft-versus-host disease after bone marrow transplantation for leukemia. *New Engl J Med* 1986; **314**: 729–735.
- Schultz KR, Nevill TJ, Toze CL *et al*. The pharmacokinetics of oral cyclosporine A (Neoral) during the first month after bone marrow transplantation (BMT). *Blood* 1997; **90** (Suppl. 1): 375B.
- McGuire TR, Honaker M, Lynch JC *et al*. Renal dysfunction associated with cyclophosphamide (CSA) prophylaxis in HLA matched sibling peripheral blood stem cell transplantation (AlloBSCT): conversion from intravenous CSA to a new oral formulation. *Blood* 1999; **94** (Suppl. 1): 334a.