Digestive Diseases and Sciences, Vol. 44, No. 4 (April 1999), pp. 775–777

A Prospective Study on Conversion from Sandimmune to Neoral in Stable Adult Liver Transplant Recipients

ASHOK JAIN, MD, MARY GADOMSKI, BSN, and JOHN FUNG, MD, PhD

Neoral is a microemulsion formulation of cyclosporin (CyA), which has more consistent and better pharmacokinetics parameters with improved bioavailability compared to conversional formulation of Sandimmune. Sixty-four stable adults (age >18 years), who had received liver transplants (LTx) and were on Sandimmune-based immunosuppression, were converted to Neoral on milligram for milligram basis. Mean age was 52.5 ± 13.5 years and male/female distribution was 22/42. Mean interval from LTx to conversion was 109.2 ± 136 months. In 13 patients (20%) the dose of Neoral was reduced because of an increase in serum creatinine ($N = 9$), hyperkalemia ($N = 1$), headache ($N = 1$), peripheral parasthesia ($N = 1$), and a general sense of discomfort ($N = 1$). Interestingly, in two patients a decrease in the trough concentration was observed with the increase in liver enzymes. Both patients responded to an increase in Neoral dose. The present study suggests while the majority of the stable liver transplant patients (77%) can be safely converted to Neoral from Sandimmune on a milligram to milligram basis, they need to be carefully monitored for renal function, liver function, and trough concentration of CyA.

KEY WORDS: liver transplantation; Sandimune; Neoral.

Neoral is an oral microemulsion formulation of cyclosporin (CyA). It has recently been approved by the FDA for clinical use. Neoral has better pharmacokinetic parameters with higher peak (T_{max}) values at a shorter period of time (C_{max}) and up to a 50% increase in the area under the concentration curve (AUC). Thus, Neoral has improved bioavailability compared to the conventional formulation of Sandimmune (1). Neoral offers more predictable trough concentration and less variability in daily trough concentration among patients and within the same patient (2). The aim of the current study was to evaluate the role of Neoral in stable adult (age >18 years) liver transplant recipients (LTx) compared to the conventional formulation of Sandimmune immunosuppression. The study examined: (1) Neoral and Sandimmune dosage, (2) changes in trough concentration of CyA, (3) changes in renal and liver function, and (4) the safety profile of drug conversion from Sandimmune to Neoral.

Manuscript received July 23, 1998; accepted October 30, 1998.

From the Thomas E. Starzl Transplantation Institute, University of Pittsburgh, Pittsburgh, Pennsylvania.

Address for reprint requests: Dr. Ashok Jain, 4th Floor, Falk Clinic, 3601 Fifth Avenue, Pittsburgh, Pennsylvania 15213.

MATERIALS AND METHODS

Sixty-four adult, stable liver transplant recipients on Sandimmune-based immunosuppression were converted to Neoral on a milligram for milligram basis. There were 22 men and 42 women. The mean age was 54.5 ± 13.5 (range 20–76) years at the time of conversion. The mean interval from LTx to conversion was 109.2 ± 136 (range 12–156; median 96) months. All patients were followed prospectively by the investigators for 12 months. The Sandimmune dose, Sandimmune trough concentration, liver function, renal function (serum creatinine and blood urea nitrogen), and electrolytes before conversion were recorded. Electrolyte, renal function, and Sandimmune trough concentration

TABLE 1

Interval from conversion	Before conversion*	After conversion*			
		1 week	1 month	6 months	12 months
CyA/Neoral dose (mg/day)	197.5	195.4	197.9	172.0	175.0
CyA level (ng/ml)	261.5	295.7	253.1	249.6	242.0
Renal function					
BUN mg/dl	25.5	26.0	25.0	26.8	26.9
Creatinine mg/dl	1.5	1.42	1.4	1.49	1.46
Serum Potassium	4.3	4.4	4.4	4.4	4.3
Liver function					
Total bilirubin (mg/dl)	1.0	0.9	0.9	0.9	1.0
ALT (units/liter)	36.0	36.0	33.5	38.5	41.7
AST (units/liter)	34.8	45.5	34.6	33.6	37.1
A P (units/liter)	109.0	89.0	109.0	103.0	94.0
GGT (units/liter)	54.0	77.0	98.0	114.0	123.0

* All values are mean values. CyA, cyclosporin; ALT, alanine aminotransferase; AST, asparted aminotransferase; GGT, gamma glutamyltransferase; AP, alkaline phosphatase.

measurements were repeated at one week after conversion. Liver function, renal function, electrolytes and Sandimmune level were reevaluated at one month and at least every two months thereafter (more often if clinically indicated) following the conversion. All adverse events were recorded carefully for next 12 months.

RESULTS

During the study period two patients died at 10 and 11.5 months after conversion (9 and 8 years after LTx, respectively). These were not considered to be related to conversion. In 13 patients (20%) the dose of Neoral was reduced because of an increase in serum creatinine ($N = 9$), hyperkalemia ($N = 1$), headache ($N = 1$), peripheral parasthesia ($N = 1$), and a general sense of discomfort ($N = 1$). All thirteen patients responded to a reduction in Neoral dose of 10–20%. Serum creatinine improved in all nine patients. Hyperkalemia, headache, parasthesia, and a general sense of discomfort were resolved. Surprisingly, in two patients there was an increase in hepatic enzymes. Both patients required an increase in Neoral dose from 75 mg/day to 100 mg twice a day in one patient, and 125 mg twice a day to 150 mg twice a day in another patient. Whole-blood trough concentration of Sandimmune was 302 ng/ml (polyclonal TDx) and 105 ng/ml (HPLC) before conversion and 211 and 74 ng/ml, respectively, after increasing the Neoral dose following the conversion. Both patients' liver functions normalized. The mean dose of Sandimmune before conversion and mean dose of Neoral after conversion with concentration is shown in Table 1. There was an 11.4% overall reduction in the dosage at 12 months after conversion. Liver function and renal function before and after conversion is shown in Table 1. There was no change in mean serum creatinine, mean blood urea nitrogen, serum bilirubin, alanine aminotransferse, aspartate aminotransferase, gamma glutamyltransferase, or alkaline phosphatase.

DISCUSSION

Controversy still exists regarding the real benefits of Neoral conversion in patients who are stable after LTx. The pharmacokinetic benefits of Neoral over Sandimmune are more obvious during the immediate postoperative period, particularly in LTx recipients who have diversion of bile through T-tube placement (3–5). Improved bioavailability is of major benefit to children compared to adults since the metabolism is faster and often requires prolonged intravenous administration of CyA (6–9). Reports of conversion to Neoral are available in kidney transplant recipients, and conversion is associated with an increase in serum creatinine and decrease in calculated creatinine clearance (10). Although the benefits of Neoral in adult recipients soon after LTx are cited in the literature, very little information is available on long-term stable adult LTx recipients (3, 4). In order to determine the safety of conversion, we developed a protocol that required initially frequent monitoring of CyA trough concentration, renal function, electrolytes, and liver functions. We followed all patients prospectively for 12 months and looked for changes in biochemical parameters and any new adverse events. Twenty percent of the patients experienced some side effects possibly related to an increase in bioavailability of CyA. However, they all responded with a reduction in neoral doses. Surprisingly, in our study two patients (3%) had a significant decrease in trough levels, resulting in deterioration in hepatic biochemical parameters. Both responded to an increased Neoral dose.

Seventy-seven percent of the adult stable liver transplant recipients were safely converted from conventional Sandimmune to Neoral without any adverse events.

REFERENCES

1. Ander L, Kahan BD: Influence of cyclosporine pharmacokinetics, trough concentrations, and AUC monitoring on outcome after kidney transplantation. Clin Pharmacol Ther 54:205–218, 1993
2. Kahn BD, Dunn J, Fitts C, Van Buren D, Wombolt D, Pollak R, Carson R, Alexander JW, Chang C, Choc M, Wong R: The neoral formulation: Improved correlation between cyclosporine trough levels and exposure in stable renal transplant recipients. Transplant Proc 26(5):2940–2943, 1994
3. Graziadei IW, Wiesner RH, Marotta PJ, Porayko MK, Dahlke LJ, Wilson SM, Steers JL, Krom RAF: Neoral compared to sandimmune is associated with a decrease in histologic severity of rejection in patients undergoing primary liver transplantation. Transplantation 64(5):726–731, 1997
4. Winkler M, Haller G, Oldhafer K, Bechstein WO, Kattner A, Maibucher A, Farber L, Burghardt R, Christian U, Neuhaus, Pichlmayer R: A new oral formulation of cyclosporine for early oral immunosuppression therapy in liver transplant recipients. Transplantation 62(6):1063–1068, 1996
5. Oldhafer K, Haller GW, Kattner A, Winkler M, Maibucher A, Farber L, Bechstein WO, Ringe B, Neuhaus P, Pichlmayr R: Absorption of cyclosporine neoral early after liver transplantation: Influence of bile on oral absorption. Transplant Proc 28(4):2237–2238, 1996
6. Jain AB, Fung JJ, Tzakis AG, Venkataramanan R, Abu-Elmagd K, Alessiani M, Reyes J, Irish W, Mehta S, Todo S, Starzl TE: Comparative study of cyclosporine and FK 506 dosage requirements in adult and pediatric orthotopic liver transplant patients. Transplant Proc 23(6):2763–2766, 1991
7. Dunn S, Cooney G, Sommerauer J, Lindsay C, McDiarmid S, Wong RL, Chang C, Smith H, Choc MG Jr: Pharmacokinetics of an oral solution of the microemulsion formulation of cyclosporine in maintenance pediatric liver transplant recipients. Transplantation 63(12):1762–1767, 1997
8. D'Agostino D, Gimenez M, Yamaguchi B, Glanczpigel R, Vinuesa F, Gamba M, Ciardullo, De Santibanes E: Conversion and pharmacokinetic studies of a microemulsion formulation of cyclosporine in pediatric liver transplant patients. Transplantation 62(8):1068–1071, 1996
9. Melter M, Rodeck B, Kardorff R, Hoyer PF, Maibucher A, Brodehl J: Successful reconversion from tacrolimus to cyclosporine a neoral in pediatric liver recipients. Trans Proc 28:2276-2278, 1996
10. Amante AJ, Meier-Kriesche H, Schoenberg L, Kahan BD: A pharmacokinetic comparison of the corn oil versus microemulsion gelcap formulation of cyclosporin used *de novo* after renal transplantation. Transplant 10:217–222, 1997