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Experience with Neoral versus Sandimmune in primary liver transplant recipients

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Abstract We compared results using Neoral versus Sandimmune, each in combination with steroid and azathioprine immunosuppression, in primary liver transplantation recipients. There were 15 patients in each group with similar demographic distributions. Intravenous cyclosporine was stopped at 4.3 ± 1.9 days in the Neoral group vs 7.8 ± 4.9 days in the Sandimmune group ($P < 0.025$). Cyclosporine levels in the first 10 days were higher (mean 306 ng/ml vs 231 ng/ml) in the Neoral group than the Sandimmune group ($P < 0.05$). The Neoral dose was less than the Sandimmune dose (mean 5.5 ng/kg per day vs 7.9 ng/kg per day) to achieve these levels in that time period ($P < 0.05$). Two patients (13%) experienced three episodes of biopsy-proven rejection in the Neoral group compared to nine patients (60%) with 12 episodes of rejection in the Sandimmune group ($P < 0.025$). Incidences of neurological and renal complications were similar between the groups. Infections requiring treatment were also similar. Liver function, renal function, and marrow function, evaluated at days 7, 14, 21, 28, and 2, 4, 6, and 12 months post-transplant, were not different between the groups. In summary, shorter use of intravenous cyclosporine and quicker stabilization of trough cyclosporine levels was achieved with Neoral than with Sandimmune. In the early post-transplant period, higher levels with lower doses were achieved with Neoral than with Sandimmune. In our experience, the incidence of rejection was lower with Neoral than with Sandimmune. There were similar lengths of hospitalization, mortality, adverse events, retransplantation, and similar liver, renal, and marrow function up to 1 year post-transplantation. Because of this experience, we continued to use Neoral in a total of 59 primary liver transplant recipients. We have not used intravenous cyclosporine in the last 44 patients. Follow-up was a mean of 11.4 months, ranging from 1 to 27 months. The incidence of rejection was 24% in these 59 patients compared to our historical experience of 70% using Sandimmune.

Key words Neoral · Sandimmune · Cyclosporine · Liver transplantation · Rejection

Introduction

The management of Sandimmune cyclosporine A therapy is challenging due to inconsistent absorption, bile dependence, and low/unpredictable bioavailability, all leading to variable blood levels and requiring frequent monitoring and dose adjustments [3, 9, 12]. The newer microemulsion formulation of cyclosporine A, Neoral, has improved and more consistent absorption, leading to a more predictable pharmacokinetic profile with a

higher peak concentration, earlier time to peak concentration, higher area under the concentration versus time curve, less intra- and inter-subject variability, better correlation of the trough level to the area under the curve, and less dependence on food intake and bile flow [2, 6, 7, 11, 13, 17, 18]. There is a need to examine the clinical effects of the more consistent exposure provided by Neoral compared to Sandimmune in a relatively homogeneous liver transplant patient population. The purpose of this study was to examine Neoral compared to Sandimmune use in primary liver transplant recipients, focusing on efficacy (rejection rate) and safety (complications, length of hospitalization).

Patients and methods

This is a single-center, prospective, comparative open label study of 30 patients receiving either Neoral or Sandimmune as part of an immunosuppressive regimen after transplantation. Inclusion criteria for this study were age over 18 years, ability to provide informed consent, stable general medical condition for 2 months prior to study entry, and primary liver transplantation as a single organ transplant. Exclusion criteria were those undergoing retransplantation, severe coexisting disease, malignancy other than incidental hepatocellular carcinoma, and patients who were United Network for Organ Sharing (UNOS) status one. This study was reviewed by the Institutional Review Board of Vanderbilt University Medical Center. The study was performed in accordance with the ethical standards laid down by the 1964 Declaration of Helsinki. Informed consent was obtained from all patients prior to inclusion in the study.

All patients received intravenous cyclosporine as a continuous infusion immediately postoperatively and the began to receive one of the two oral formulations, Sandimmune or Neoral, as soon as they were able to tolerate oral intake. The intravenous formulation was discontinued as soon as possible after beginning the oral medication, tapering to maintain therapeutic blood levels (200–300 ng/ml). Oral medication was taken at 12-h intervals. Other immunosuppressive medications were also administered. Azathioprine was dosed at 1.5 mg/kg per day but adjusted to maintain white blood cell count at $> 5000/mm^3$. Methylprednisonolone was given 1000 mg intraoperatively, 200 mg on the first postoperative day tapering to 30 mg on day 6 and 15 mg at 3–6 months. Demographic data were recorded prior to transplantation. Blood specimens were collected and laboratory studies recorded preoperatively and at days 7, 14, 21, and 28, and months 2, 4, 6, and 12 post-transplantation for hematological studies, serum chemistry studies, and cyclosporine levels.

Diagnosis of acute rejection required documentation using standard criteria by liver biopsy [1]. Complications and adverse events were recorded over a 1-year period and included those resulting in death, disability, prolonged hospitalization, and documented infection. Serum chemistries were evaluated to monitor hepatic, renal, and marrow function. Patients were followed for 1 year unless withdrawn due to either death or retransplantation. Follow-up was complete in all patients. Data were summarized using mean and standard error of the mean. Nominal data were compared by χ^2 analysis while continuous data were compared by Student's t-test.

Results

There were 30 patients, 15 receiving Neoral and 15 receiving Sandimmune. The mean age was comparable, 46 ± 11 years in the Neoral group and 41 ± 11 years in the Sandimmune group. The gender distribution was not significantly different, 60% male in the Neoral group and 73% male in the Sandimmune group. The weight in the 15 patients receiving Neoral was a mean of 85 ± 13 kg and a mean of 88 ± 13 kg in the 15 patients receiving Sandimmune. The distribution of underlying disease was similar: chronic active hepatitis 10 versus 12 patients; alcoholic liver disease 2 versus 2 patients; fulminant hepatic failure 1 versus 0 patients; primary biliary cirrhosis 1 versus 1 patient; and Wilson's disease 1 versus 0 patients. The severity of liver disease assessed by the Childs-Pugh classification was similar in the two groups: Class A 2 versus 2; Class B 6 versus 5; and Class C 7 versus 8. Severity assessed by UNOS status was also similar between the Neoral and Sandimmune groups: status one 0 versus 0; status two 1 versus 0; status three 8 versus 10; and status four 6 versus 5. The mean UNOS status was 3.3 ± 0.6 in the Neoral group and 3.3 ± 0.5 in the Sandimmune group. The distribution of ABO compatibility was similar between the groups as well: ABO identical 12 versus 15; ABO compatible 3 versus 0; and ABO incompatible 0 versus 0.

The immunosuppressive protocols used in the two groups were the same. Cyclosporine, azathioprine, and corticosteroids were used in 14 patients in each group. OKT3 induction was used in one patient in each group.

Intravenous cyclosporine was stopped at a mean of 4.3 ± 1.9 days in the Neoral group, shorter than the 7.8 ± 4.9 days in the Sandimmune group ($P < 0.025$). The dosing of the two study medications and the cyclosporine trough levels in the two groups are demonstrated in Fig. 1.

The initial length of hospital stay was 15 ± 9 days for the Noral group versus 14 ± 6 days for the Sandimmune group. The median length of stay was 13 versus 14 days. After the initial hospitalization, 11 patients required 17 readmissions for an average of 6 ± 6 days in the Noral group; in the Sandimmune group 10 patients required 24 readmissions for an average of 7 ± 9 days.

Table 1 demonstrates a lower rate of rejection in the Neoral group than in the Sandimmune group ($P < 0.025$). It also demonstrates fewer episodes of rejection in the Neoral group. No episode of rejection in these 30 patients was steroid resistant. The table displays the distribution of rejection over time.

One patient each in the Neoral and Sandimmune groups was withdrawn from further study due to death on day 6 from right heart failure and on day 9 from cardiopulmonary arrest, respectively. Additionally, one patient in the Neoral group was withdrawn at day 125 and two in the Sandimmune group at days 99 and 109 as

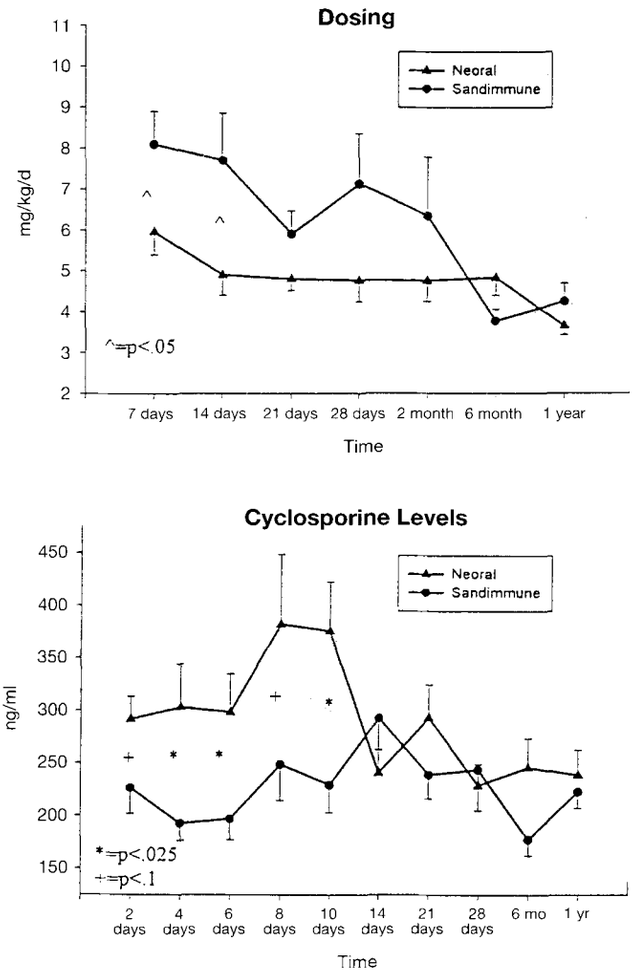


Fig. 1 Cyclosporine dosing and cyclosporine levels in the first year after primary liver transplantation in patients receiving Neoral or Sandimmune. The dose of Sandimmune was higher than Neoral in the first 2 months, reaching statistical significance in the first 14 days. Despite the difference in this dosing, cyclosporine levels were higher in the patients receiving Neoral than those receiving Sandimmune in the first 10 days but were equivalent for the remainder of the first year

they required retransplantation for hepatic artery thrombosis.

Complications within the first year after transplantation were not different between the two study groups. Central nervous system and peripheral nervous complications were noted in four Neoral and five Sandimmune patients. Dialysis was required in no Neoral patient and in two Sandimmune patients. The white blood cell count did not decline below 3000 in any patient and the platelet count declined below 30000 in two Sandimmune patients. Bacterial infections, documented by culture and treated by medication, were noted in 13 Neoral patients versus 20 Sandimmune patients. Fungal infections were noted in two Neoral patients and in three patients receiving Sandimmune. Viral infections were documented in six patients receiving Neoral versus ten patients receiving Sandimmune. Comparison of hepatic functional parameters (Fig. 2), renal functional parameters (Fig. 3), and marrow function (Fig. 4) are presented for the first year after transplantation.

Table 1 Rejection in first year after transplantation

	Neoral	Sandimmune	*P*
Patients	2 (13%)	9 (60%)	< 0.025
Episodes			
< 7 days	1	4	
8–14 days	1	4	
14–28 days	0	2	
29–182 days	1	2	
182–365 days	0	0	
Total	3	12	< 0.025

Discussion

The study groups were not different with regard to demographics, disease as the indication for transplantation, severity of liver disease, ABO compatibility or immunosuppressive regimen. There was no difference in the number of infections or other complications, in the initial length of hospital stay or in readmissions. Both cohorts of patients exhibited similar hepatic, renal, and marrow function within the first postoperative year. However, a difference was found with respect to the requirements for intravenous cyclosporine.

The rejection rate was significantly lower when Neoral was administered. Both the number of patients suffering rejections and the total number of rejection episodes were reduced in the cohort receiving Neoral immunosuppression. The lower rate of rejections seen in the Neoral group (13%), compared to the Sandimmune group (60%) may be related to increased cyclosporine exposure resulting from improved absorption and an improved pharmacokinetic profile following Neoral administration. Other investigators have reported a lower incidence of rejection with Neoral use in liver transplantation recipients. In an open-label, multicenter, clinical study completed in the United Kingdom, Jamieson [5] found a 37% rejection incidence in 20 primary liver recipients receiving Neoral compared to a 70% rejection rate in historical controls receiving Sandimmune. Hemming et al. [4], reporting their experience in 41 consecutive liver recipients, found a similar reduction in rejection incidence (25% versus 65%) in a comparative trial using Neoral and Sandimmune. In a large study involving 166 primary liver transplant recipients, the rejection incidence was 30% and 66% in patients receiving Neor-

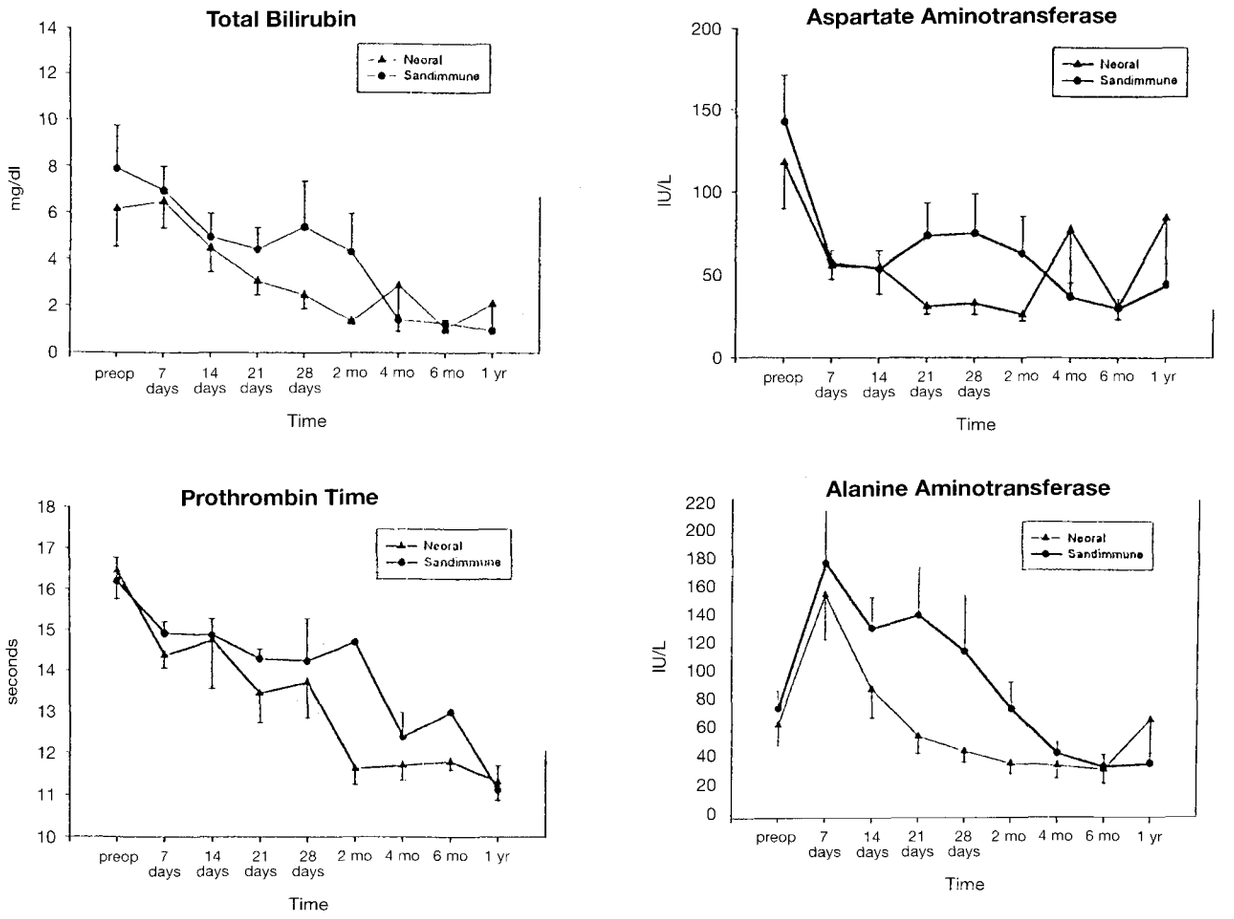
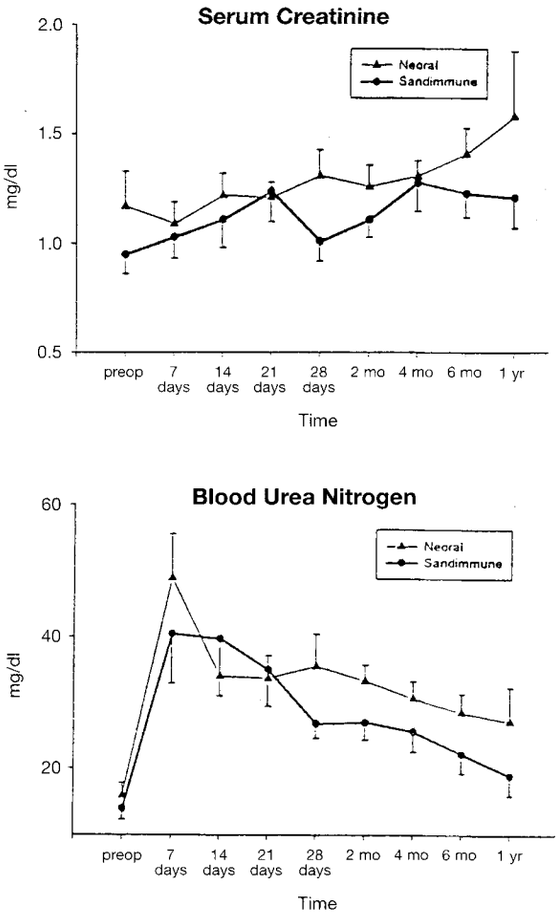


Fig. 2 Comparison of four hepatic parameters in primary liver transplant recipients receiving Neoral or Sandimmune. There were no statistically or clinically significant differences in total bilirubin, prothrombin time, aspartate aminotransferase or alanine aminotransferase within the first year. Although not shown, there were also no differences in serum alkaline phosphatase levels within the first year

al and Sandimmune, respectively [10]. In another clinical trial [15], 25 consecutive primary liver recipients were administered Neoral via a nasogastric tube within 6 h of transplantation. A reduction in rejection rate (24% vs 52%) was realized when compared to historical controls. Additionally, pharmacokinetic monitoring demonstrated that immediate postoperative dosing of Neoral was correlated with adequate cyclosporine systemic exposure within 48 h of surgery.

Steady cyclosporine levels were achieved more rapidly with oral administration of the Neoral formulation, allowing earlier discontinuation of intravenous cyclosporine in the Neoral group compared to Sandimmune. Neoral administration included a preoperative dose, 5 mg/kg, and a postoperative dose of 10–15 mg/kg per day on a twice-daily schedule. This dose range was necessary to achieve target trough levels within 48 h postoperatively. Cyclosporine levels tended to be higher using lower doses in the Neoral group than in the Sandimmune group. The Neoral dose was relatively stable throughout the study while the Sandimmune dose decreased over the year (see Fig. 1). Cyclosporine is a highly lipophilic compound; bile flow [9, 12], gastrointestinal motility [17], and co-administration of food [3] impact upon its absorption. These limitations in the original cyclosporine oral formulation (Sandimmune) preclude its early use following liver transplantation. Absorption of the microemulsion formulation (Neoral) is less bile dependent and more consistent, thus yielding systemic exposures of cyclosporine which are sevenfold higher than those resulting from Sandimmune administration [7]. Intravenous cyclosporine may not be required after liver transplantation since Neoral is well absorbed, even when given via nasogastric tube, thus providing smooth cyclosporine induction. This avoids the nephrotoxic side-effects and costs associated with intravenous administration of cyclosporine. Subsequent to



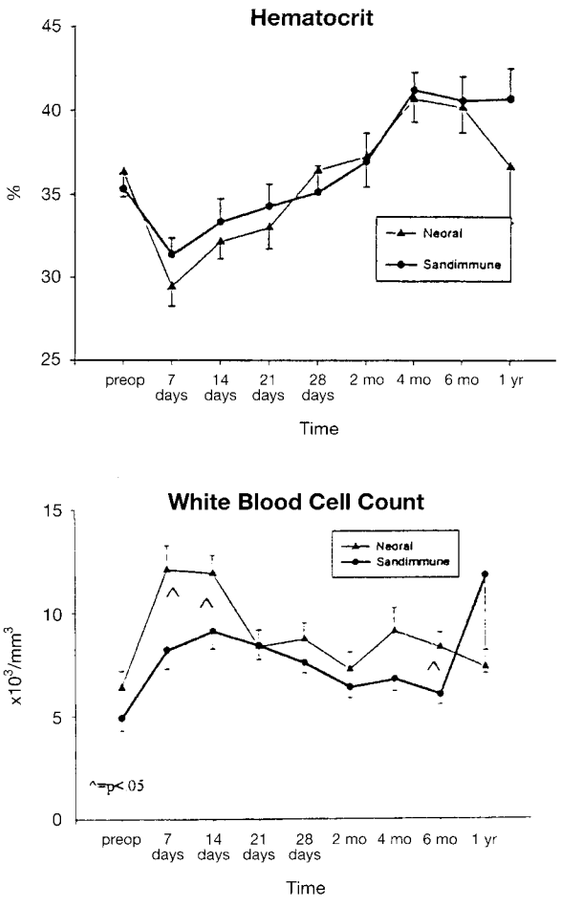


Fig. 3 Serum parameters of renal function in primary liver transplant recipients receiving Neoral or Sandimmune within the first year. There were no statistically significant differences between the two groups

this trial, intravenous cyclosporine has not been required for 44 liver transplant recipients. Postoperative doses of 10–15 mg/kg per day in divided doses yielded trough levels within the putative therapeutic range. The 59 liver transplant recipients receiving Neoral immunosuppression have been followed from 1 to 27 months (mean 11.4 ± 10.0 months) and only 14 of 59 (24%) have suffered allograft rejection episodes. Historically, the rejection incidence occurring in our liver recipients immunosuppressed with Sandimmune is 70%.

Investigators have noted the increased absorption of Neoral, abrogating the necessity for intravenous cyclosporine. Winkler et al. [19] administered incremental doses of Neoral under an umbrella of intravenous cyclosporine in 20 patients. In the subsequent 30 patients, Neoral was administered immediately postoperatively at a dose of 12–15 mg/kg per day without

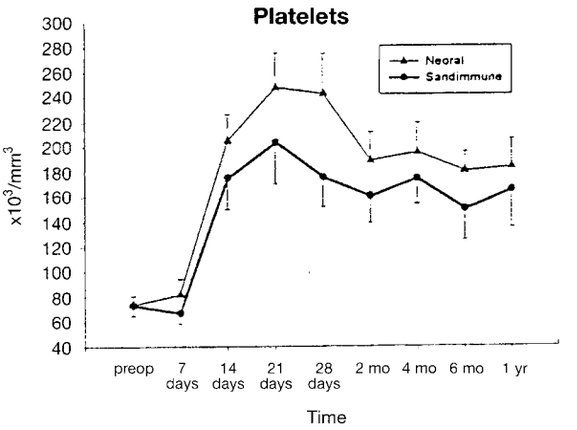


Fig. 4 Morrow function in primary liver transplant recipients receiving Neoral or Sandimmune within the first year. The while blood cell count was significantly higher in the Neoral group than in the Sandimmune group on days 7 and 14. The higher platelet count in the Neoral group seen throughout the first year did not reach statistical significance

initiation of intravenous cyclosporine. Only three patients in this cohort required intravenous cyclosporine therapy to achieve adequate levels. Other investigators [4, 15, 16] have corroborated our findings that the initiation dose of Neoral postoperatively is 12–15 mg/kg per day and that intravenous cyclosporine is typically not required.

The improved immunosuppressive efficacy with Neoral use was not associated with a higher rate of untoward side effects. There are several clinical studies [4, 15, 19] supporting our findings, reporting similar rates of complications after primary liver transplantation with the use of Neoral versus Sandimmune. Levy and colleagues [7, 8] reported a reduction in rejection rates with a similar safety profile in patients receiving either Sandimmune or Neoral. The occurrence of adverse effects including hypertension, nephrotoxicity, neurotoxicity or lymphoproliferative disease was similar. Several single-center and multicenter trials evaluating the efficacy and safety of Neoral versus Sandimmune have demonstrated a similar safety profile with respect to mortality rate, retransplantation incidence, and occurrence of adverse events [4, 14, 15, 19]. Neoral appears to increase a patient's systemic exposure to cyclosporine, thus reducing the risk of rejection without altering the safety profile associated with cyclosporine.

References

1. Demetris AL, Qian S, Sun H, Fung JJ (1990) Liver allograft rejection: an overview of morphologic findings. Am J Surg Pathol 14: 49–63
2. Drewe J, Meier R, Vonderscher J, Kiss D, Psanski U, Kissel T, Gyr K (1992) Enhancement of the oral absorption of cyclosporine in man. Br J Clin Pharmacol 34: 60–64
3. Gupta SK, Benet LZ (1989) Absorption kinetics of cyclosporine in healthy volunteers. Biopharm Drug Dispos 10: 591–596
4. Hemming AW, Grieg PD, Caltral MS, Chung SW, Lilly LB, Aljumah AA, Levy G (1996) A microemulsion of cyclosporine without intravenous cyclosporine in liver transplantation. Transplantation 62: 1798–1802
5. Jamieson NV (1995) Neoral: the new microemulsion formulation of cyclosporine. World Medical Press, Cedar Knolls, NJ, pp 34–39
6. Kahan BD, Dunn J, Fitts C, Van Buren D, Wombolt D, Pollak R, Carson R, Alexander JW, Choc M, Wong R, Hwang DR (1995) Reduced inter- and intrasubject variability in cyclosporine pharmacokinetics in renal transplant recipients treated with a microemulsion formulation in conjunction with fasting, low-fat meals, or high-fat meals. Transplantation 59: 505–511
7. Levy G, Rochon J, Freeman D, Wong P-Y, Banks L, Roach C, Engel K, Grant D (1994) Cyclosporine Neoral in liver transplant recipients. Transplant Proc 26: 2949–2952
8. Levy G, Altraif I, Rezieg M, Asfar S, Rochon J, Freeman D, Wong P-Y, Banks L, Roach C, Engel K, Grant D (1994) Cyclosporine Neoral in liver transplant recipients. Transplant Proc 26: 3184–3187
9. Mehta MU, Venkatataramanan R, Burckart GJ, Ptachcinski RJ, Delamos B, Stachak S, Van Thiel DH, Iwatsukis TE (1988) Effect of bile on cyclosporine absorption in liver transplant patients. Br J Clin Pharmacol 25: 579–584
10. Mirza DF, Gunson BK, Soonawalla Z, Mayer AD, Buckels JA, McMaster P (1997) Reduced acute rejection after liver transplantation with Neoral-based triple immunosuppression. Lancet 349: 701–702
11. Mueller EA, Kallay Z, Kovarik JM, Richard F, Weisinger O, Schmidt K, Scheele J (1995) Bile-independent absorption of cyclosporine from a microemulsion formulation in liver transplant patients. Transplantation 60: 515–517
12. Naoumov NV, Tredger JM, Steward CM, O'Grady JG, Grever J, Niven A, Whiting B, Williams R (1989) Cyclosporine A pharmacokinetics in liver transplant recipients in relation to biliary T-tube clamping and liver dysfunction. Gut 30: 391–396
13. Ohlman S, Lindholm A, Hagglund H, Sawe J, Kahan BD (1993) On the intraindividual variability and chronobiology of cyclosporine pharmacokinetics in renal transplantation. Eur J Clin Pharmacol 44: 265–269
14. Pinson CW, Beauregard-Zollinger L (1996) Interim analysis of study OLN-356: Neoral versus Sandimmune in US primary liver transplant recipients. Transplant Proc 28: 2234–2236
15. Rasmussen A, Hjortrup A, Hasen B, Heslet L, Kirkegaard P (1996) Induction of immunosuppression by microemulsion cyclosporine in liver transplantation. Transplantation 62: 1031–1033
16. Tredger JM (1995) Using cyclosporine Neoral immediately after liver transplantation. Ther Drug Monit 17: 638–641
17. Trull AK, Tan KKC, Uttridge J, Tredger JM (1993) Cyclosporine absorption from microemulsion formulation in liver transplant recipients. Lancet 341: 433
18. Trull AK, Tan KKC, Tan L, Alexander GJM, Jamieson NV (1994) Enhanced absorption of new oral cyclosporine microemulsion formulation, Neiral, in liver transplant recipients with external biliary diversion. Transplant Proc 26: 2977–2978
19. Winkler M, Haller G, Oldhafer K, Bechstein WO, Kattner A, Mabucher A, Farber L, Ringe B, Christians U, Neuhaus P, Pichlmayr R (1996) A new oral formulation of cyclosporine for early oral immunosuppression therapy in liver transplant recipients. Transplantation 62: 1063–1068