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New strategies to optimize clinical outcomes with cyclosporine in liver transplantation

G.A. Levy

Director, Multi Organ Transplant Program. Toronto General Hospital. University of Toronto. Toronto. Ontario.

INTRODUCTION

The introduction of the immunosuppressive agent, cyclosporin A (CsA) revolutionized our approach to transplantation[1]. Not only did the use of this agent lead to increased patient and graft survival following renal transplantation, but its introduction allowed the successful implementation of liver, lung, heart and pancreas transplant programs[2]. Incomplete, high intra- and interpatient variability and unpredictable and inconsistent absorption of Sandimmune limited the use of this galenic formulation and necessitated the need for intra venous CsA early in the post transplant period[3]. This approach resulted in increased neuro and renal toxicity limiting the clinical usefulness of this agent. To preclude toxicity, therapeutic drug monitoring was initiated initially by measurement of trough blood levels (C_0)[4]. This approach was largely adopted to limit toxicity, although C_0 was subsequently studied for its ability to predict freedom from rejection[5]. The introduction of the microemulsion formulation Neoral improved a number of the problems associated with the use of the previous galenic formulation, Sandimmune[6-8]. Its use resulted in less intra and interpatient variability, improved absorption and less dependence on bile for absorption especially early in the post operative period[9]. Studies demonstrated that Neoral is absorbed more uniformly from the intestine than Sandimmune, providing a closer correlation between dose and exposure assessed in area under the time concentration curve (AUC)[10]. However, it soon became apparent that the correlation between trough levels and AUC although markedly better for Neoral than Sandimmune was still insuffcient to reflect AUC by itself[11]. The introduction of Neoral as a superior formulation of CsA has led to an interest in evaluating the traditional approach to therapeutic drug monitoring of CsA based on trough levels[12].

Correspondencia: Dr. G.A. Levy
Director, Multi Organ Transplant Program. Toronto General Hospital.
University of Toronto. 621 University Avenue. 10NU-116.
Toronto. Ontario M5G 2C4.
Correo electrónico: glfgl2@attglobal.net

Therapeutic drug monitoring strategies

For drugs with a low therapeutic index (narrow window between efficacy and toxicity) which are utilized in critically ill patients, whose status is changing over time, it is appreciated that therapeutic drug monitoring (TDM) is essential[13]. To this end, applied pharmacokinetics, that is a strategy by which dosing regimens for patients are guided by repeated measurements of blood drug concentrations must be adopted. Drug concentrations are then adjusted to keep patients within a defined target concentration range. Intuitively, drug concentrations above the target range are defined as toxic and below the range as sub therapeutic.

CO monitoring

Initial TDM of CsA utilized samples drawn at trough, namely, the time immediately before the next dose is administered (C_{min}). On examination of C_{min} records from patients experiencing toxic complications of CsA therapy, a serum trough level of 250 ng/ml was established as the upper limit of the putative therapeutic window. The lower limit of the therapeutic window was assumed to correspond to the dose of CsA necessary to cause a 50% inhibition of an in-vitro mixed lymphocyte reaction and was found to be 100 ng/ml. Utilizing C_0, it soon became apparent that measurements did not consistently predict freedom from rejection or drug toxicity (table I). Thus, studies were undertaken to determine if other monitoring strategies could be utilized to define parameters to differentiate efficacy and toxicity.

TABLE I. **Failure of correlation between trough levels (TL): rejection versus toxicity/non-selective serum RIA**

TL Serum (ng/ml)	N	Rejection	NTX or HTX
< 100	16	0.025	NS
≥	40	NS	0.001

Reproduced from Kahan BD, et al. Trans Proc 1984;16:1195-9.

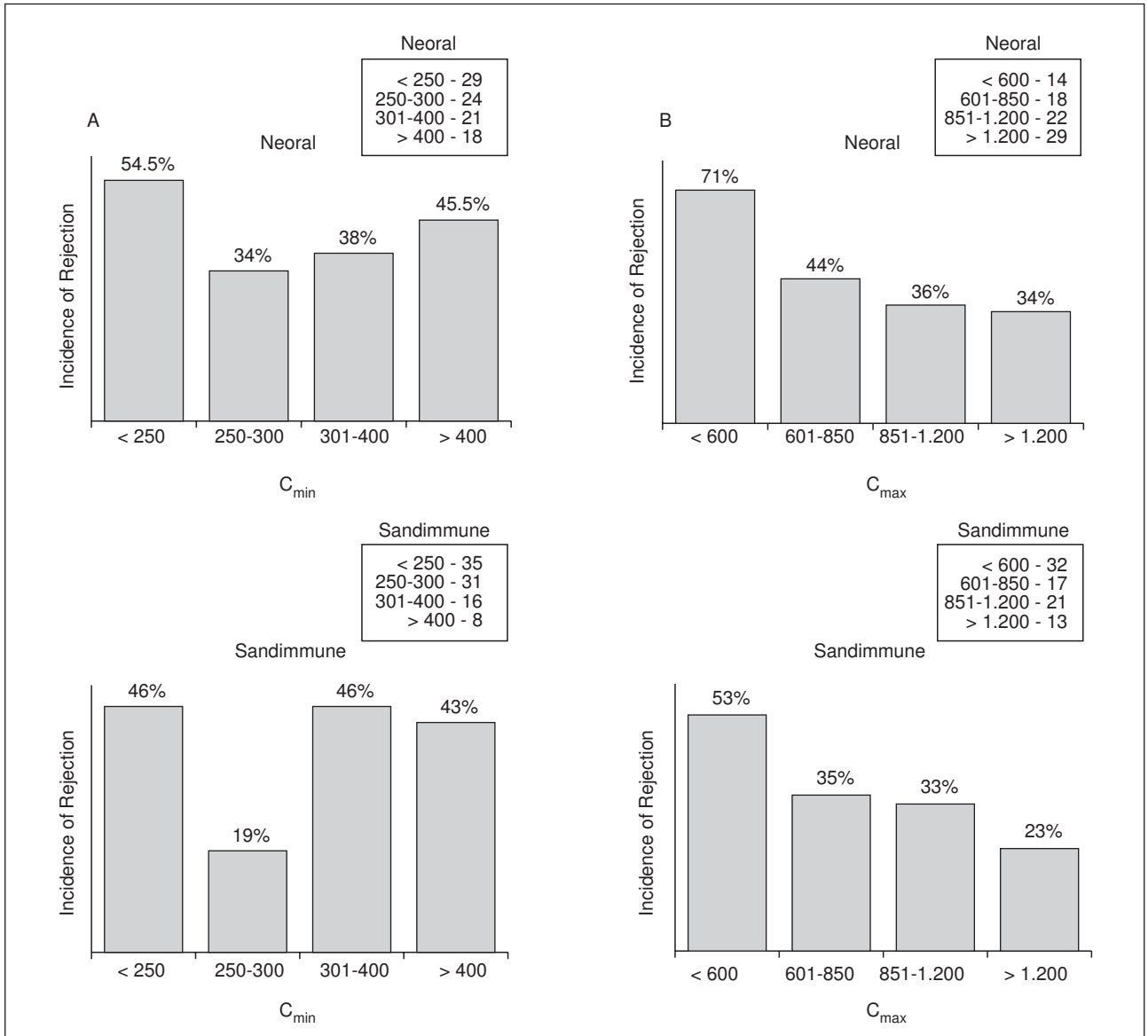

Fig. 1. Relationship between rejection and cyclosporine blood levels. Patients were randomized to receive Sandimmune or Neoral. Retrospectively, patients were divided into four equal C_{min} or C_{max} quartiles and incidence of rejection was analyzed. CsA levels were monitored by C_{min} (trough). Incidence of rejection was analyzed in patient cohorts in relation to (A) C_{min} or (B) C_{max} (reproduced from Grant D, et al[22]).

Area under the time concentration curve (AUC) monitoring

Kahan et al has provided evidence that full AUC monitoring in kidney transplant recipients is the most sensitive and precise indicator of drug exposure[14,15]. In his pivotal studies, it was clearly shown that large inter and intra patient variability in CsA pharmacokinetic parameters, bioavailability and clearance rate correlated with poor patient and graft outcome[16].

Abbreviated AUC monitoring

As full AUC monitoring proved impractical, attempts were made to use sparse sampling models for estimation of AUC[17,18]. It was shown that the use of three sampling points could estimate full AUC with high precision and predict freedom from acute and chronic rejection with 95% accuracy[17-19]. More recently, use of two points (2 and 6 hours post dose) was highly predictive of the absorption phase of AUC and correlated with freedom from rejection[20,21].

Concentration 2 hour after intake (C_2) monitoring Neoral Formulation Study 8 (NOF-8)

A pivotal prospective study conducted in liver transplant recipients demonstrated that measurements of C_{max} in contrast to C_{min} (trough, C_0) correlated with freedom from

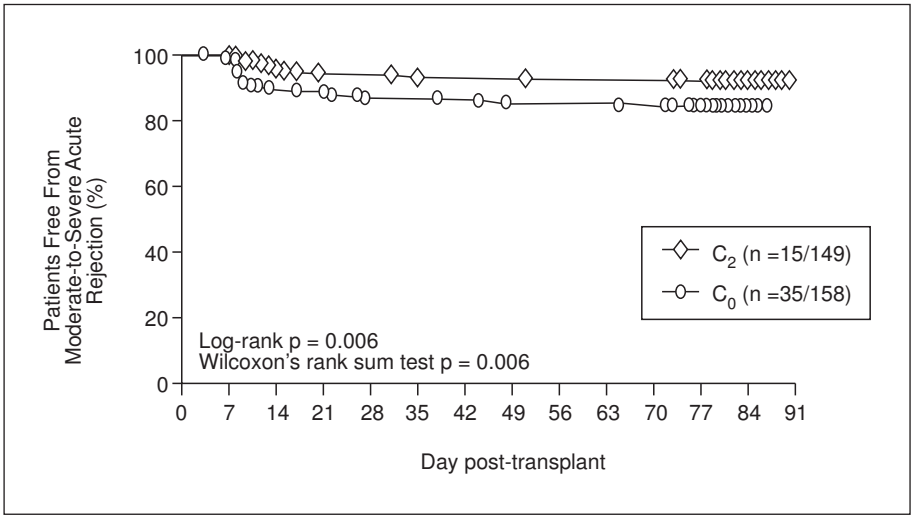

Fig. 2. Cyclosporin microemulsion (Neoral) concentrations at 2 hours after administration (C_2) up to 91 days post-transplantation in liver transplant recipients. C_2 monitoring results in a significant reduction in rejection severity compared with pre-dose trough concentration (C_0) monitoring. (reproduced from Levy GA, et al[25]).

rejection[22]. Rejection rates in Neoral treated patients who achieved C_{max} values greater than 800 ng/ml were 34% (fig. 1). A similar relationship was seen in patients who received Sandimmune, however, as compared with Neoral fewer patients receiving Sandimmune achieved high C_{max} reflected absorption difficulties with Sandimmune in liver transplant recipients. In contrast, patients who achieved C_{max} levels less than 600 ng/ml has rejection rates of 71%. In patients who received Neoral, C_2 proved to be an excellent surrogate marker of AUC 0-6 and C_{max} ($r^2 = 0.93$), whereas no relationship between C_0 (trough level) and freedom from rejection was observed, even when C_0 approached or exceeded 450 ng/ml. The relationship of C_2 with C_{max} was less strong in the early post operative period (< 5 days) but it was excellent thereafter.

This study provided an important pharmacokinetic correlation of C_2 with acute rejection in liver transplant recipients. Not only was the sampling point C_2 and accurate predictor of the AUC for Neoral treated patients, but there was strong correlation between C_2 concentrations and incidence of acute rejection and provided an impetus for additional studies to evaluate the role of C_2 as TDM tool in both the acute and maintenance phases of liver transplantation

INT-06 Study

The reliability of C_2 monitoring as a tool for optimizing Neoral administration has now been evaluated in a prospective, multicentre, open-label international study[23]. This study was designed to compare the utility of monitoring Neoral therapy by C_2 versus C_0 in *de novo* liver transplant patients. The target CsA range for the C_2 group (n = 149) between 0 and 3 months post transplant was 0.80 to 1.2 ug/m and for the C_0 cohort (n = 158) was 250 to 400 ng/ml. At 3 months post transplantation, the C_2 group of patients had a 25% reduction in the percentage of patients with acute rejection compared with the C_0 group (23.6 versus 31%) $p < 0.006$ (fig. 2). In those patients who achieved C_2 target values by day 3-5 post transplantation, the incidence of acute cellular rejection was reduced to 12.5%. The incidence of moderate to severe acute rejection was significantly lower than in the C_2 monitored group ($p = 0.01$). Furthermore, when HCV patients were excluded from the analysis, patients monitored by C_2 had a highly statistically significant reduction in the incidence and severity of rejection ($p < 0.03$). By Cox Regression Analysis, it was shown that only C_2 and not dose or C_0 levels correlated with rejection (table II). It was important to note that patients monitored by C_2 did not have an increase in serious adverse events. This is the first prospective clinical trial to clearly show the superiority of monitoring by C_2 versus C_0.

TABLE II. **Effect of predictor variables on primary outcome as analysed by the Cox Regression Model**

Variable	Coefficient	SE (coef)	z	p
Dose (mg/kg)	–0.046409	0.033154	–1.400	0.1616
C_0 (ng/ml)	0.000212	0.000503	0.422	0.6731
C_2 (µg/ml)	–0.000985	–0.000247	–3.985	0.0001

SE (coef): standard error (coefficient); z: coefficient/SE (coefficient); C_0: trough CsA concentration; C_2: CsA concentration at 2 hours post-dose. Proceding from Levy GA, et al[23].

Effect of Achieving C2 Early

More recent studies have now been conducted at the University of Toronto to examine the effect of achieving C_2 target values (0.8 to 1.2 µg/ml) within 3 to 5 days of transplantation on the incidence of rejection and renal in *de novo* liver transplant recipients[24]. In 30 *de novo* transplant recipients, cyclosporin microemulsion administration was initiated at 15 mg/kg/day in divided doses and adjustments to C_2 target values were made according to the following formula:

New daily dose = old daily dose X target level desired/level measured

By day 3,80% of patients achieved target levels and by day 5 all patients achieved target levels using an aggressi-

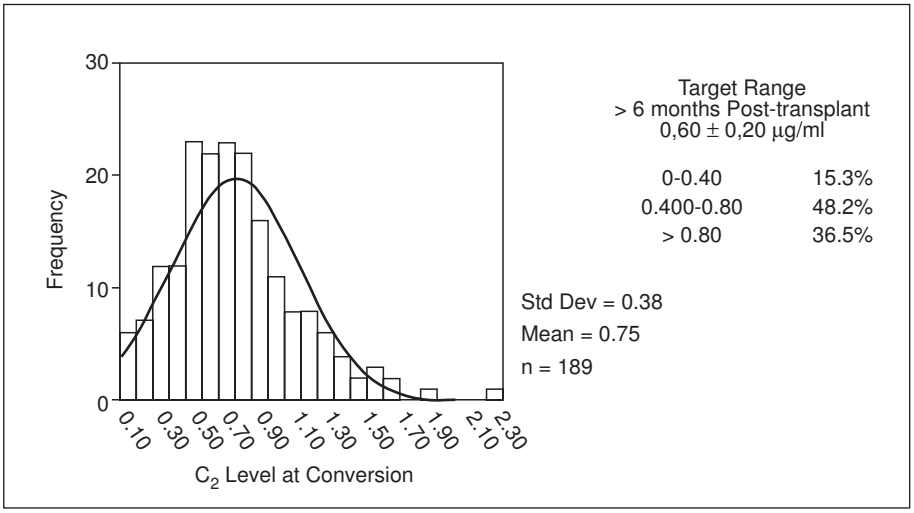

Fig. 3. C_2 levels in maintenance liver transplant patients monitored by C_0. At time of adoption of C_2, the mean C0 was 198 ng/ml (range 96-482 ng/ml) and the mean C_2 was 0.88 µg/ml (range 0.114-1.90 µg/ml). Thirty-three percent (33%) of patients had C_2 levels exceeding recommended targets, and 18% of patients had C_2 levels below target. There was a poor correlation between C_0 and C_2 ($r^2 = 0.19$).

ve drug administration strategy as outlined. No apparent renal toxicity was observed, with serum creatinine levels remaining within normal ranges (< 110 µmol/l). An overall incidence of rejection of 7% (2/30 patients) was observed and in the 2 patients who experienced rejection, the rejection was mild and reversed by a single course of high dose steroids.

C_2 in Maintenance Phase

Recently we have reported short term results of conversion of liver transplant patients in the maintenance phase from C_0 monitoring to C_2 monitoring[25]. In that study, conversion of maintenance liver transplant patients to C_2 monitoring resulted in an improvement in renal function, reduction in the incidence and severity of diabetes mellitus and hypertension with no improvement in serum cholesterol. Our center has now converted 351 patients on Neoral who were a minimum of 3 months post-transplant and we now provide data on these patients with a mean follow up of 15 months (range 9-24 months). One hundred and ninety-one (191) of the patients were male and 160 female with an average age of 50.2 ± 11.6 years (10 to 71.2 years) at the time of transplantation. At the time of conversion, the mean C_0 was 164 ng/ml (range 92 to 482 ng/ml); the mean C_2 at time of conversion was 740 ng/ml (range 114 to 1900 ng/ml). There was a poor correlation between C_0 and C_2 ($r^2 = 0.14$). Thirty-six percent (36%) of patients at time of conversion had C_2 levels exceeding recommended targets (0-6 months, 1,000 ng/ml; 6-12 months, 800 ng/ml; > 12 months, 600 ng/ml) (fig. 3). Within 3 months of conversion to C_2 there was a mean decrease in serum creatinine of 26%: pre-conversion 161 µmol/l (range 70-284 µmol/l); post-conversion mean of 134 µmol/l (range 60-272 µmol/l) ($p < 0.001$). A similar improvement in blood pressure was seen with C_2 adjustment to target (mean decrease in diastolic pressure of 16 ± 3 mmHg) ($p < 0.001$). An improvement in serum cholesterol (normal range 4.6-6.2 mmol/l) which was not previously seen in our early follow-up, was observed (pre-conversion 7.4 ± 1.8 mmol/l; post-conversion 6.1 +/-1.4 mmol/l) To achieve target, a mean dose reduction of 16% (range 4-26%) was required ($p < 0.04$). In 62 patients, once day dosing was adopted with C_2 monitoring resulting in an improvement in renal function and a reduction in hypertension with no adverse events seen. No clinical or biochemical evidence of rejection was seen during dose adjustments. This study provides further evidence of the advantages of conversion of maintenance liver transplantation to C_2 monitoring resulting in improvement in renal function, hypertension, diabetes and disturbances in cholesterol.

TABLE III. **Neoral C2 correlates best with AUC_{0-4} in all transplant patient groups**

Organ	Author	AUC_{0-4} Correlation (r^2)	
		C_2	C_0
Renal	Mahalti[20]	0.81	0.18
Liver	Grant[22]	0.93	-
Heart	Cantarovich*	0.82	0.41
Paediatric renal	Kelles**	0.81	0.41
Paediatric liver	Dunn***	0.89	0.03

*Cantarovich et al. Clin Transplant 1998;12:243-9. **Kelles et al. Pediatr Transplant 1999;3:283-7. ***Dunn et al. Am J Transplant 2001.

Summary

In summary, the introduction of Neoral has allowed investigators to examine alternative therapeutic drug monitoring strategies to improve liver transplant patient outcomes. C_2 monitoring in the liver transplant recipient has been identified as a sensitive predictor of acute cellular rejection in *de novo* liver transplant recipients in a multi-center prospective trial. Furthermore, in long term transplant recipients, adoption of C_2 monitoring results in a reduction in toxicity including nephrotoxicity, incidence of diabetes and hypertension and disturbances in lipid metabolism. C_2 monitoring has now been shown to correlate best with AUC_{0-4} in all trans-

plant patient groups and also correlates with rejection (table III). Collectively these data demonstrate the superiority of monitoring liver transplant patients taking Neoral by C_2 monitoring and provide a rationale for its adoption by the transplant community.

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