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C2 is superior to C0 as predictor of renal toxicity and rejection risk profile in stable heart transplant recipients

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Summary

To assess whether cyclosporine A (CsA) 2-h peak (C2) is superior to trough levels (C0) for Neoral dose monitoring in heart transplantation (HT), we studied 928 C0–C2 paired determinations from 313 stable HT patients (257 male, aged 50 ± 14 years at HT, follow-up 6.9 ± 4 years), on a C0-based regimen. Our target C0 levels (ng/ml) were 150–400 (first 3 months), 150–300 (4–12 months), 100–250 (>12 months). Mean C0 and C2 levels were 268 ± 80 and 1031 ± 386, respectively (first 3 months); 230 ± 49 and 955 ± 239 (4–12 months); 157 ± 53 and 745 ± 236 (>12 months). For patients within the target C0, the corresponding C2 were 600–1500 (first 3 months), 600–1300 (4–12 months), 400–1100 (>12 months). C2 correlated with C0 ($r = 0.64$, $P = 0.0001$). C2 correlated better with CsA dose than C0 ($r = 0.41$, $P = 0.0001$ vs. $r = 0.33$, $P = 0.0001$). Between patients, CsA dose varied by a factor of 9.3; the C/dose ratio varied by a factor of 8.5 for C2 and of 15.6 for C0. Patients with higher C2 (>740) had higher severe rejection score at 2 years ($P = 0.02$) than patients with lower C2. This did not apply to C0. Both C2 and C0 correlated with blood urea ($r = -0.18$, $P = 0.0001$; $r = -0.12$, $P = 0.0002$) and creatinine ($r = -0.19$, $P = 0.0004$; $r = -0.19$, $P = 0.0001$ respectively). By logistic regression higher C2 (>740) was associated with higher total severe rejection score at 2 years ($P = 0.006$). C2 showed better correlation with CsA dose, renal function, rejection profile and less variability between patients than C0. C2 may improve CsA-based immunosuppression in HT.

Introduction

Cyclosporine A (CsA) has a low therapeutic index, requiring blood concentration monitoring, which is routinely based on trough-level (C0) [1–3]. The new CsA formulation, Neoral, provides higher and less variable systemic exposure compared with the old formulation (Sandimmune), as assessed by the shape of the area under the concentration–time curve (AUC) [4]. However, drug exposure, that is maximal up to 4 h after a dose of Neoral (AUC_{0-4}), correlates poorly with C0 [5,6]. In addition, AUC_{0-4} is invasive and impractical for routine use [7]. Several studies investigated Neoral concentration at various single time points to identify surrogate markers for AUC_{0-4} [5,6,8–12]. They reported that the 2-h post-dose sampling point (C2) was the most accurate single-point marker in various transplanted organs, including heart [5,9–12]. Recent clinical trials indicate positive correlation of C2 levels with probability of freedom from acute rejection in *de novo* renal and liver transplants

[6,13–17]. In addition, initial data suggest correlation of C2, but not of C0, with chronic rejection, as well as beneficial effects on renal function, in long-term renal and liver transplants, switched to C2 monitoring [7,18–20]. This has lead to consensus guidelines in favor of converting kidney and liver recipients to C2 monitoring, using predefined target levels [21,22]. In heart transplantation (HT) C2 target levels were not yet been established by controlled trials [9,23–26]. In addition, two recent studies failed to show a strong correlation of C2 with AUC in patients on Neoral alone or Neoral plus diltiazem [27,28]. These workers suggested further evaluation before applying C2 in HT [27,28]. the aim of the present cross-sectional study was to assess whether C2 is superior to C0 as predictor of rejection risk and renal toxicity in a homogeneous cohort of long-term HT patients on standard C0 monitoring.

Methods

Patients and study protocol

From October 3, 2001 to July 31, 2002 we collected 928 C0-C2 paired determinations from 313 stable HT recipients (257 male, mean age at HT 50 ± 14 years); mean post-HT follow-up was 6.9 ± 4 years (range: 1 month–12 years). CsA had been taken at the same dosage for at least 1 week prior to blood sampling. C2 blood samples were taken at 2 h ± 15 min postdose, concomitantly with the patients' routine follow-up visits, which included clinical cardiological examination, 12-lead electrocardiogram, chest X-ray, routine blood chemistry (including blood creatinine, and urea), two-dimensional and Doppler echocardiogram every 6–12 months or when clinically indicated, coronary angiography every year. The CsA daily dose was adjusted based on C0 target levels, as well as on the patient's renal function (assessed by blood creatinine). Our target C0 levels were 150–400 ng/ml (first 3 months), 150–300 (4–12 months), 100–250 (>12 months). C0 and C2 were measured by monoclonal immunoassay (CEDIA; Roche Diagnostics, Milan, Italy) [21,29]. The local Ethics Committee approved the study and each patient gave informed consent.

Baseline immunosuppression

HT recipients were on CsA and azathioprine (Aza) (double therapy), or with CsA, Aza and oral prednisone (PDN) (triple therapy). Starting in September 1997 all patients had been converted from Sandimmune to Neoral and all *de novo* cases had received Neoral. Oral PDN was associated to CsA and Aza in the presence of repeated or persistent rejection or of CsA nephrotoxicity. Induction immunosuppression included a single dose of CsA (5 mg/kg) and of Aza (3 mg/kg) administered 6 h before operation, and a bolus of methylprednisolone (MethPD) (1000 mg i.v.) during cardiopulmonary bypass. Immunosuppression was started on the day of operation with increasing doses of CsA up to 2–12 mg/kg/day and of Aza up to 0.5–2 mg/kg/day. The Aza dose was adjusted to maintain a total white blood cell count of at least 4000/mm^3. Postoperatively, the majority (83%) of patients had received antilymphocyte (ALG) and/or antithymocite globulin (ATG) for 3–5 days. Graft rejection was monitored by endomyocardial biopsy following established protocols (weekly during the first month, biweekly until the third month, monthly until the first year; in the presence of grade 2 rejection, in the following 10–15 days). Endomyocardial biopsies were obtained via the right internal jugular vein (Caves–Schultz bioptome). At least four adequately sized specimens from each patient were fixed in 10% phosphate buffered formalin (pH 7.35%); 7 μm paraffin embedded serial sections were cut, stained according to the hematoxylin–eosin technique and graded according to the International Society for Heart and Lung Transplantation (ISHLT) standardized grading system [30]. Acute rejection episodes, defined as ISHLT grade >2, were treated with i.v. administration of methylprednisolone, combined with ALG or ATG in the presence of symptoms.

Rejection scores and cumulative immunosuppressive doses

Rejection scores (RS) were assigned based on a modification of the ISHLT grading as follows: 1A = 1, 1B = 2; 2 = 3, 3A = 4, 3B = 5, and 4 = 6, and were used in risk factor analysis [30,31]. The following RS were calculated for each patient: RS in the total follow-up (TRS); RS in the first and second year (RS 1 year, RS 2 years); TRS including only severe grades (≥3A) (sev-TRS); first year and second year RS including only severe grades (sev-RS 1 year; sev-RS 2 years). All scores were normalized for the number of biopsies taken in each patient. Cumulative doses (mg/kg) of CsA, Aza, PDN and MethPD at 3, 6, 12 months, and cumulative total steroid load in the first year were calculated. Cumulative PDN load of each patient in the first year (PDN 1 year) was calculated in mg/kg, as well as cumulative MethPD (MethPD1 year), and total steroid load (TotCORT 1 year = PDN 1 year + MethPD1 year), following conversion of each MethPD dose to an equivalent PDN dose (4 mg of MethPD = 5 mg of PDN) [31].

Statistical analyses

Data were analyzed with SPSS software version 10.1 (1999; SPSS, Inc., Chicago, IL, USA). Results are

expressed as mean ± SD, unless otherwise specified. Student's *t*-test or ANOVA were used to compare mean values. The ordinal data were analyzed by chi-square test. $P < 0.05$ was considered to be significant. Pearson's test was used to correlate paired data. Multivariate analysis for high C2 and C0 was performed by logistic regression. Variables included in multivariate analysis for high C0 and C2 were recipient sex and age at HT, number of treated rejections at 1 year, RS 1 year, RS 2 years, TRS, sev-TRS, sev-RS 1 year; sev-RS 2 years, baseline blood urea and creatinine, cumulative CsA, Aza, PDN, MethPD1 year, TOTCORT1 year dosages (mg/kg) at 3, 6, and 12 months.

Results

Frequency, distribution and correlations of C0 and C2 levels

Of the 313 study patients, in whom the 928 C0-C2 pairs were obtained, 19 were in the first 3 months (group A), 10 in the following 9 months (group B), and 284 were more than 12 months post-HT (group C). Demographic features are given in Table 1 and were similar among groups. CsA daily dose was higher in groups A and B than in group C. Mean C0 and C2 (ng/ml) levels were 268 ± 80 and 1031 ± 386, respectively (group A); 230 ± 49 and 955 ± 239 (group B); 157 ± 53 and 745 ± 236 (group C). For patients within the target C0 the corresponding C2 were 600–1500 (first 3 months, 15 patients), 600–1300 (4–12 months, nine patients), 400–1100 (>12 months, 210 patients). C2 correlated with C0 (Pearson, $r = 0.64$, $P = 0.0001$) (Fig. 1). C2 correlated better with CsA daily dose (mg/kg) than C0 ($r = 0.41$, $P = 0.0001$ vs. $r = 0.33$, $P = 0.0001$) (Fig. 2). Between patients, CsA dose varied by a factor of 9.3; the C/dose

Table 1. Demographic features in HT study patients at study entry.

	Group A ($n = 19$)	Group B ($n = 10$)	Group C ($n = 284$)	*P*-value
Mean age at HT (years)	49 ± 8	48 ± 7	50 ± 14	NS
Sex (male/female)	16/3	8/2	233/51	NS
Body weight (kg)	68 ± 15	75 ± 16	75 ± 16	NS
CsA daily dose (mg/kg)	3.9 ± 1.4	4.3 ± 2.7	2.9 ± 1.1	0.0001
Blood urea (mmol/l)	10 ± 5	13 ± 6	13 ± 6	NS
Blood creatinine (μmol/l)	123 ± 37	148 ± 57	170 ± 99	NS

Group A, 1–3 months; group B, 4–12 months; group C, >12 months.

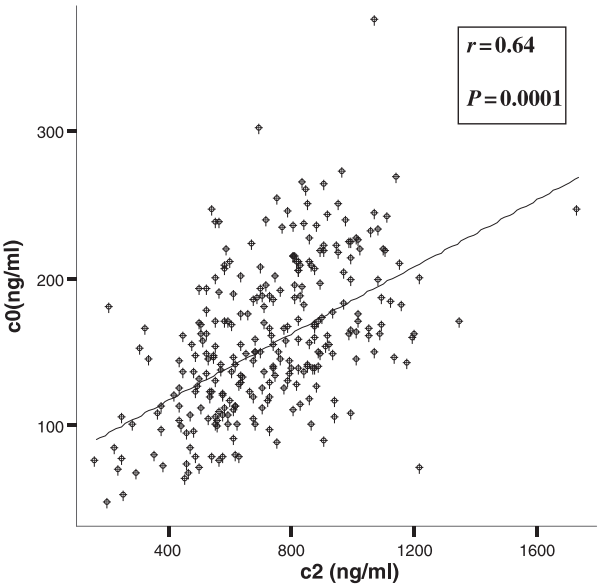

Figure 1 Direct correlations of C2 and C0 levels (Pearson's test).

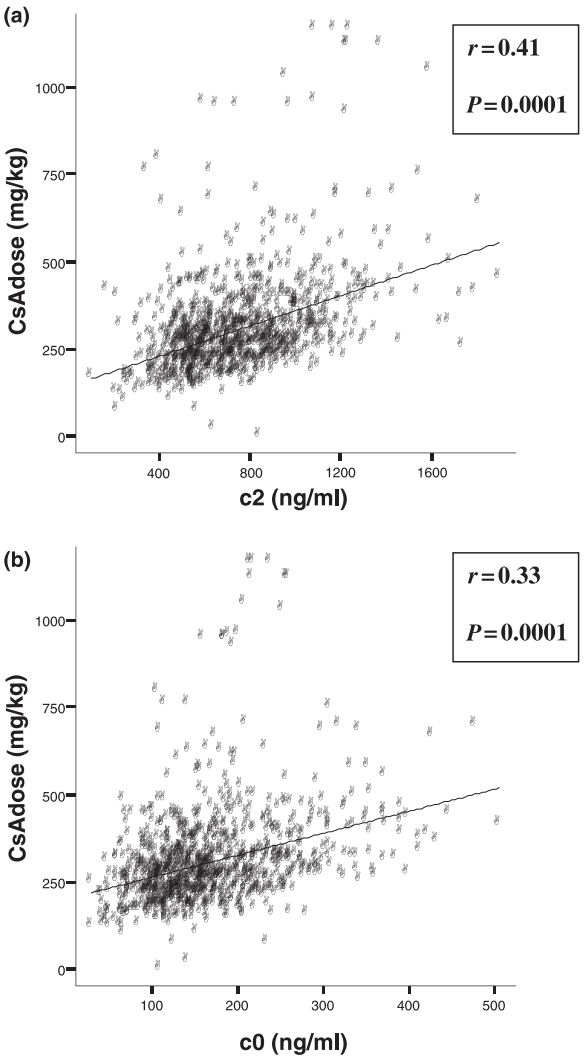

Figure 2 Direct correlations of (a) C2 levels and CsA daily dose and (b) C0 and CsA daily dose (Pearson's test). C2 correlates better than C0 with CsA daily dose.

ratio varied by a factor of 8.5 for C2 and of 15.6 for C0. Both C2 and C0 correlated with blood urea ($r = -0.18$, $P = 0.0001$; $r = -0.12$, $P = 0.0002$, respectively; Fig. 3) and creatinine ($r = -0.19$, $P = 0.0004$; $r = -0.19$, $P = 0.0001$, respectively; Fig. 4).

C0 and C2 levels as predictors of rejection risk and renal dysfunction by univariate and logistic regression analysis

Complete data sets were available for analysis in 269 (95%) of the 284 patients with follow-up ≥12 months (Tables 2–4). Median values of C0 and C2 in the 269 patients were used as cutoffs (150, 740 ng/ml, respectively), in order to divide the study patients into similar groups. Clinical features in patients with and without high C0 (≥150, <150, respectively; Table 2) and with or without high C2 (≥740, <740, respectively; Table 3) were compared on the first pair of C0–C2 determinations.

High C0 levels were associated with a shorter follow-up ($P = 0.003$), a higher CsA daily dose ($P = 0.004$), higher number of treated rejection episodes in the first year

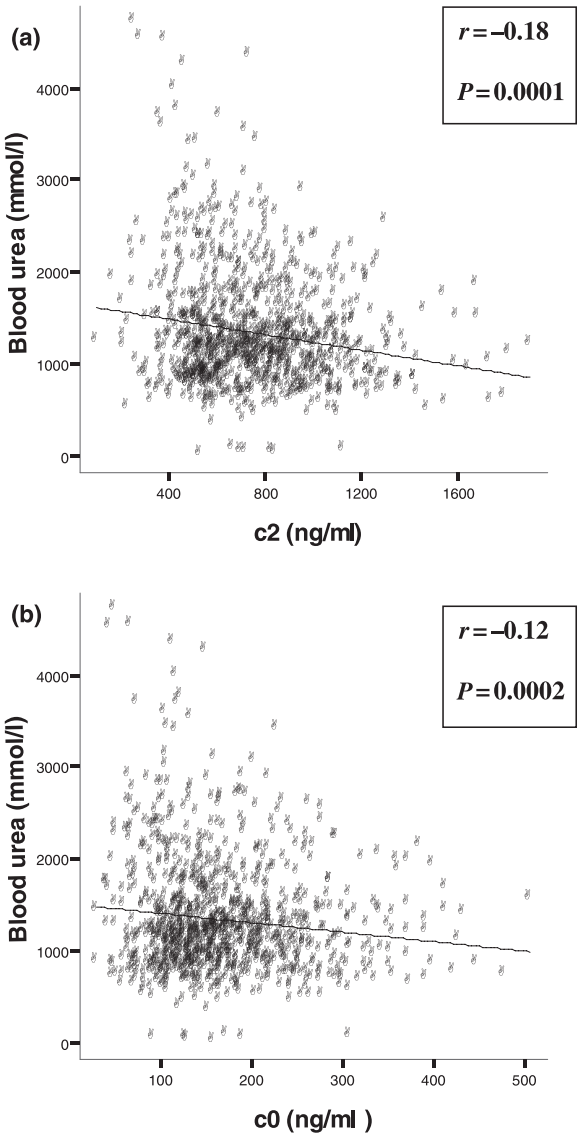

Figure 3 Inverse correlations of (a) C2 levels and blood urea and (b) C0 and blood urea (Pearson's test). C2 correlates better than C0 with blood urea.

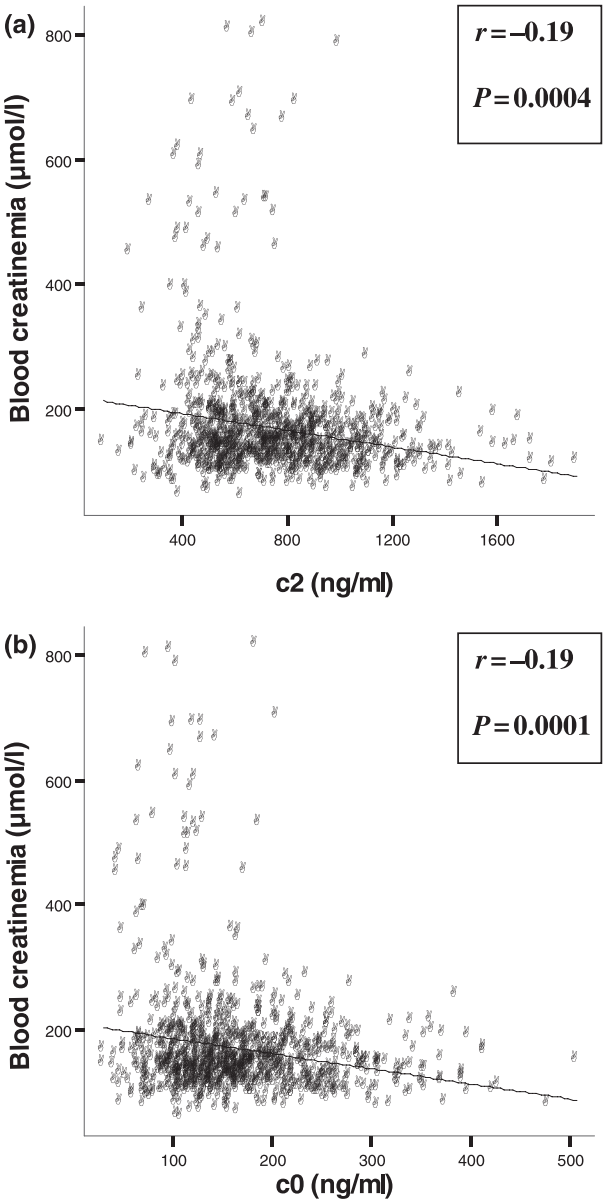

Figure 4 Inverse correlations of (a) C2 levels and blood creatinine and (b) C0 and blood creatinine (Pearson's test). C2 and C0 show similar correlations with blood creatinine.

Table 2. Comparison of baseline features in patients with and without high C0 by univariate analysis.

	Patients with high C0 ($n = 136$)	Patients with low C0 ($n = 133$)	*P*-value
Recipient age at HT (years)	50 ± 15	48 ± 17	NS
Follow up (years)	7.1 ± 3.6	8.4 ± 3.7	0.003
Sex (M/F)	116/20	109/24	NS
Idiopathic cardiomyopathy pre HT [n (%)]	60 (44)	58 (44)	NS
Ischemic cardiomyopathy pre HT [n (%)]	51 (37)	53 (40)	NS
CsA daily dose/kg baseline (mg/kg)	3 ± 1	2.6 ± 1	0.004
Diabetes post-HT [n (%)]	22 (16)	20 (15)	NS
Hypertension post-HT [n (%)]	110 (81)	104 (78)	NS
Hypercolesterolemia post-HT [n (%)]	83 (61)	78 (59)	NS
Angiographic ejection fraction (%)	62 ± 7	61 ± 9	NS
CsA at 3 months (mg/kg)	586 ± 271	618 ± 531	NS
CsA at 6 months (mg/kg)	1142 ± 501	1157 ± 1018	NS
CsA at 1 year (mg/kg)	2105 ± 883	2109 ± 1754	NS
Aza at 3 months (mg/kg)	137 ± 80	152 ± 76	NS
Aza at 6 months (mg/kg)	255 ± 158	271 ± 157	NS
Aza at 1 y (mg/kg)	478 ± 324	503 ± 313	NS
PDN at 3 months (mg/kg)	14.1 ± 11	13 ± 12	NS
PDN at 6 months (mg/kg)	25 ± 19	23 ± 22	NS
PDN at 1 y (mg/kg)	39 ± 29	36 ± 33	NS
MethPD1 year (mg/kg)	76 ± 64	78 ± 65	NS
TOTCORT1 year (mg/kg)	135 ± 91	133 ± 92	NS
Treated rejections (≥3A) in the first year (n)	1.95 ± 1.7	1.54 ± 1.3	0.04
Total treated (≥3A) rejections (n)	2.1 ± 1.8	1.7 ± 1.4	NS
Blood urea at baseline (mmol/l)	12.7 ± 5	14.5 ± 7.5	0.02
Blood creatinine at baseline (μmol/l)	157 ± 70	192 ± 129	0.007
TRS	1.11 ± 0.61	1.22 ± 0.79	NS
RS 1 year	1.20 ± 0.7	1.32 ± 0.85	NS
RS 2 year	0.84 ± 0.83	0.73 ± 0.72	NS
sev-TRS	0.13 ± 0.12	0.15 ± 0.13	NS
sev-RS 1 year	0.15 ± 0.14	0.17 ± 0.15	NS
sev-RS 2 year	0.045 ± 0.01	0.043 ± 0.01	NS

High C0, ≥mean value (≥150 ng/ml); low C0, mean value (<150 ng/ml).
Aza, azathioprine; PDN, prednisone; MethPD, methylprednisolone; TOTCORT, total steroid load; CAV, coronary allograft vasculopathy; CsA, cyclosporine A; F, female; HT, heart transplantation; M, male; RS 1 year, rejection score in the first year; sev-RS 1 year, rejection score in the first year including only severe grades; sev-RS 2 year rejection score in the second year including only severe grades; sev-TRS, rejection score in the total follow-up including only severe grades (≥3A); TRS, rejection score in the total follow-up; NS, not significant.

($P = 0.04$), as well as lower baseline blood urea ($P = 0.02$) and creatinine ($P = 0.007$) (Table 2).

High C2 levels were associated with a shorter follow-up ($P = 0.0001$), a higher CsA daily dose ($P = 0.001$) and a higher cumulative load of PDN at 1 year ($P = 0.03$), higher number of treated rejection episodes in the whole follow-up ($P = 0.04$), as well as lower baseline blood creatinine ($P = 0.005$) (Table 3).

Results of logistic regression analysis are detailed in Table 4. High C2 (>740) levels were associated with higher total severe rejection score at 2 years ($P = 0.006$, relative risk 12.4, 95% confidence intervals 2–75.8). The remaining variables included in the analysis did not reach statistical significance. No significant associations were found with higher C0 (>150) (not shown).

Discussion

C2 levels in stable HT patients on C0 monitoring

The C2 target levels have not yet been established in heart transplant recipients, although tentative targets have been suggested based upon retrospective or single-center experience on small adult patient numbers [9,23–26]. In addition, two recent studies on stable HT recipients on Neoral therapy, although confirming the poor correlation of C0 with AUC, failed to show a strong correlation of C2 with AUC in patients on Neoral alone or Neoral plus diltiazem [27,28]. These workers suggested further evaluation before applying C2 monitoring in long-term stable HT recipients, as it might lead to inappropriate dose adjustments of CsA in

Table 3. Comparison of baseline features in patients with and without high C2 by univariate analysis (≥12 months follow up)

	Patients with high C2 ($n = 129$)	Patients with low C2 ($n = 140$)	*P*-value
Recipient age at HT (years)	50 ± 15	48 ± 17	NS
Follow up (years)	6.7 ± 3.4	8.7 ± 3.7	0.0001
Sex (M/F)	106/23	119/21	NS
Idiopathic cardiomyopathy pre HT [n (%)]	55 (43)	63 (45)	NS
Ischemic cardiomyopathy pre HT [n (%)]	49 (38)	55 (39)	NS
CsA daily dose/kg baseline (mg/kg)	3.1 ± 1	2.6 ± 1	0.001
Diabetes post-HT [n (%)]	19 (15)	23 (16)	NS
Hypertension post-HT [n (%)]	99 (77)	115 (82)	NS
Hypercolesterolemia post-HT [n (%)]	80 (62)	82 (58)	NS
Angiographic ejection fraction (%)	61 ± 9	62 ± 7	NS
CsA at 3 months (mg/kg)	580 ± 245	621 ± 529	NS
CsA at 6 months (mg/kg)	1110 ± 452	1184 ± 1016	NS
CsA at 1 year (mg/kg)	2069 ± 846	2139 ± 1732	NS
Aza at 3 months (mg/kg)	146 ± 84	143 ± 74	NS
Aza at 6 months (mg/kg)	274 ± 168	253 ± 148	NS
Aza at 1 year (mg/kg)	526 ± 350	461 ± 286	NS
PDN at 3 months (mg/kg)	14.5 ± 11.5	13.2 ± 11.5	NS
PDN at 6 months (mg/kg)	26.3 ± 20	22 ± 20	NS
PDN at 1 year (mg/kg)	43 ± 30	33 ± 30	0.03
MethPD1 year (mg/kg)	80 ± 70	74 ± 60	NS
TOTCORT1 year (mg/kg)	143 ± 98	126 ± 84	NS
Treated rejections (≥3A) in the first year (n)	1.9 ± 1.6	1.6 ± 1.4	NS
Total treated (≥3A) rejections (n)	2.2 ± 1.8	1.7 ± 1.4	0.04
Blood urea at baseline (mmol/l)	13 ± 5	14.5 ± 7.5	NS
Blood creatinine at baseline (μmol/l)	156 ± 67	192 ± 127	0.005
TRS	1.18 ± 0.61	1.18 ± 0.79	NS
RS 1 year	1.27 ± 0.7	1.25 ± 0.80	NS
RS 2 years	0.91 ± 0.79	0.67 ± 0.62	0.03
sev-TRS	0.13 ± 0.11	0.15 ± 0.13	NS
sev-RS 1 year	0.16 ± 0.14	0.16 ± 0.15	NS
sev-RS 2 year	0.05 ± 0.01	0.03 ± 0.01	NS

High C2, ≥mean value (≥740 ng/ml); low C2, mean value (<740 ng/ml).
See Table 2 for expansion to abbreviations.

Table 4. Multivariate analysis for high C2 (≥740 ng/ml in HT patients ($n = 269$).

Variable	*P*-value	RR	95% CI
Recipient age >50	NS		
Recipient male sex	NS		
Baseline creatinine	NS		
Baseline urea	NS		
Number of treated rejections in the first year	NS		
TRS	NS		
RS 1 year	NS		
RS 2 years	NS		
sev-TRS	NS		
sev-RS 1 year	NS		
sev-RS 2 years	0.006	12.4	2–75.8
CsA at 3 months (mg/kg)	NS		
CsA at 6 and 12 months (mg/kg)	NS		
Aza at 3, 6, 12 months (mg/kg)	NS		
PDN at 3, 6, 12 months (mg/kg)	NS		
MethPD1 year, TOTCORT1 year (mg/kg)	NS		

See Table 2 for expansion to abbreviations.

patients receiving concomitant metabolic inhibitors [27,28]. In the present study we assessed clinical correlates of C0 and C2 concentrations on a large data set of 928 paired observations, as well as univariate and multivariate predictors of high C0 and C2 levels in a homogeneous cohort of stable long-term HT patients, managed on the routine C0 monitoring. In addition, during the study period none of our patients were receiving diltiazem, metabolic inhibitors, itraconazolum or new immunosuppressive drugs, e.g. mycophenolic acid, that, influencing CsA levels, might be confounding factors [27,28]. The Neoral dose used in our long-term HT patients was approximately 3.0 mg/kg/day, and is therefore similar to that used by previous studies on C2 in HT [9,23,24]. The median C2 level that we found as cutoff (>740 ng/ml) for high C2 is close to the upper target range (600 ng/ml) used by Cantarovich *et al.* [9,23,24]. Our data are comparable with those of Cantarovich *et al.* because our Neoral doses are slightly

higher and no conversion of C2 target values is needed between the EMIT used by Cantarovich *et al.* [9,23,24] and the CEDIA techniques used by us [21]. We found that there was a relatively poor correlation between C0 and C2 (Pearson, $r = 0.64$, $P = 0.0001$), in spite of the large data set of paired C0–C2 measurements, that might have reduced the weight of confounding factors, such as the presence of poor absorbers [7].

C0 and C2 levels: associations with clinical and diagnostic features

Our results on univariate analysis showed that both high C0 and C2 levels were associated with shorter follow-up, higher Neoral daily doses, better indexes of kidney function and higher number of treated rejection episodes. In addition, high C2 was associated with higher prednisone cumulative load. These findings are in keeping with the design of our study. In fact, we did not make any dose adjustments based on C2, but dose changes were made looking at our C0 targets, clinical and echocardiographic findings, as well as as renal function tests and follow-up duration. Thus, long-term HT patients were kept on the lowest Neoral dose that was associated with stable renal function; Neoral dose was lowered empirically in the presence of worsening renal tests. This explains both the inverse associations and the negative correlations of C0, C2 with renal indexes. The progressive Neoral dose reduction with the lengthening of follow-up is in keeping with our clinical practice of tapering down immunosuppression after the first year, when rejection risk is lower [32], to reduce long-term side effects of CsA, particularly nephrotoxicity [33,34]. This explains the inverse association we found in C0 and C2 levels as well as in Neoral daily doses with follow-up time. Overall, our results of univariate analysis and the correlation data show that C2 performs better than C0, e.g. the C/dose ratio varied by a factor of 8.5 for C2 and of 15.6 for C0. This finding has important clinical implications because CsA maximal concentration is higher with Neoral than with Sandimmune [4]. The higher CsA peak in patients treated with Neoral may account for the transient higher incidence of renal dysfunction in transplant patients monitored with C0, which was observed during the first 6 months after conversion from Sandimmune [6,35]. Thus, the conversion from C0 to C2 monitoring, or to a combined C0 and C2 algorithm, may have substantial advantages in terms of optimal rejection control and reduction of side effects, particularly nephrotoxicity. Our results are in keeping with the initial promising results reported by Cantarovich *et al.* [9,23,24].

C2 levels and rejection risk profile

Recent clinical trials indicate both positive correlation of C2 levels with probability of freedom from acute rejection [6,15,16] and a reduced incidence and severity of acute rejection in *de novo* renal and liver transplants, managed on a C2-based monitoring [13–15,17]. Conversely, another finding of our study is the association of both high C0, and C2 with higher number of treated rejection episodes, and of high C2 with high cumulative load of prednisone in the first year. Our interpretation of this apparently intriguing finding is twofold. First, as we always used C0 monitoring, which is poor predictor of CsA absorption [5,6], we failed to identify the 'poor absorbers' which are likely to be also at higher risk of rejection. Thus, based on the rejection history of the patient, we used higher CsA dose and higher C0, even in the long-term, in patients considered 'high rejectors' vs the 'low rejectors'. As shown, as C0 and C2 are related, this clinical practice leads to the association of high C2 with higher rejection scores. The association of high C2 with high cumulative load of prednisone in the first year is not surprising, because at our institution we use a steroid-sparing protocol [36], and, after the first 6 months, we discontinued prednisone in patients who were identified as 'low rejectors'. On the contrary, 'high rejectors' are likely to be on higher C0 target level and on triple therapy with prednisone, at 1 year as well as in the long-term. By multivariate analysis, high C2, but not C0, was an independent predictor of severe (≥3A) cumulative rejection score late in the second post-HT year. This again indicates that C2 is a better predictor of rejection profile than C0.

Conclusion

We found that C2 showed better correlation with CsA dose, renal function, rejection profile and less variability between patients than C0. C2 may improve CsA-based immunosuppression in HT, but prospective and randomized trials, based on anticipated benefits of a combined clinical outcome, are needed to define the optimal C2 targets after HT.

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