

## Lake Louise Consensus Conference on Cyclosporin Monitoring in Organ Transplantation: Report of the Consensus Panel

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The immunosuppressive action of cyclosporin A (CsA, Sandimmun) is currently thought to be initiated after uptake in lymphocytes by intracellular binding to cyclophilin, a peptidyl-prolyl isomerase. The CsA-cyclophilin complex selectively binds and inhibits the action of the serine/threonine phosphatase calcineurin, thus reducing nuclear translocation of the cytoplasmic subunit of the nuclear factor of activated T cells to the nuclear subunit, with subsequent impairment of T-cell receptor transcription of the interleukin 2 (IL-2) gene (1). In view of the complexity of these steps, the question arises as to whether blood CsA levels can predict functional impairment of lymphocyte alloreactivity and the incidence of rejection. Efforts are therefore being made to develop strategies for pharmacodynamic monitoring of CsA, such as measuring the inhibition of calcineurin (2). On the other hand, because of the substantial variation in CsA bioavailability, metabolism, and excretion, individualization of dosage without the knowledge of blood CsA

levels is difficult and may expose patients to an increased risk of either CsA underdosage or toxicity.

This meeting represents a review and critical appraisal of the recommendations and guidelines established at a previous consensus conference on the monitoring of the immunosuppressive drugs held at Minaki, Ontario, in 1990.

### RECOMMENDATIONS AND GUIDELINES

1. Whole blood is the preferred matrix for CsA measurement.
2. Ethylene diaminetetraacetic acid (EDTA) is the preferred anticoagulant.
3. The analytic method should be specific for the parent drug.
4. To validate and maintain the quality of the method for measuring CsA, participation in an external quality-assurance program is essential.
5. Trough concentrations of CsA should be determined. Sampling times should be standardized to within 1 h before the next dose.
6. Information as to the amount and time of administration of the last dose should be submitted together with the request for CsA determination.

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7. In the immediate posttransplant period, the recommended frequency of monitoring is once every 24 to 48 h.
8. The laboratory should be able to provide same-day turnaround during the early post-transplant period.
9. CsA concentrations need to be interpreted in conjunction with other laboratory data, clinical considerations, and concomitant immunosuppressive therapy.
10. In the majority of clinical situations, the monitoring of CsA metabolites is not warranted.
11. There is a need to develop assay systems capable of measuring the individual patient state of immunosuppression.

#### SAMPLE-COLLECTION TIME AND PHARMACOKINETIC MONITORING

Whole blood with EDTA as anticoagulant is the preferred matrix for CsA measurement. Whenever possible, peripheral venopuncture sampling should be preferred over sampling from a resident central venous line or capillary testing. It is also important to note that CsA displays a circadian variation, evening trough levels being significantly lower than morning trough levels (3).

The marked intra- and interindividual variation in cyclosporin pharmacokinetics (4,5) complicates effective immunosuppressive therapy. There is a poor correlation between CsA dose and whole blood trough concentration. Early investigations of the therapeutic window of CsA documented that CsA trough levels far outside a therapeutic range tended to predict adverse events (4). The relation between cyclosporin trough concentration and immunosuppressive efficacy or toxicity after organ transplantation has been widely studied (6), and currently most centers use trough CsA blood concentrations as a guide for the dosage of this drug.

However, patients displaying trough concentrations within a putative CsA therapeutic range are not always spared from either rejection or nephrotoxicity (7). In an attempt to understand the pharmacokinetic factors critical to outcome, a concentration-controlled strategy (8) based on serial concentration-time profiles was applied to determine appropriate drug doses. Because of variations intrinsic to the conventional oral liquid and gel cap formulations of CsA, this strategy was based on establishing a range of drug concentrations during continuous intravenous infusion and after oral ad-

ministration. This range of concentrations allowed identification of optimal targets during therapy: steady-state concentrations of 400  $\mu\text{g/L}$  during i.v. and initial 1-month average concentrations of 550  $\mu\text{g/L}$ , tapering to a target of 400  $\mu\text{g/L}$  from 6 to 12 months (9). Strategies using 3-point samplings seem to yield reasonable estimates of actual AUC (10) and in practice have proven equally efficient as full 7-point profiles (0, 2, 4, 6, 10, 14, and 24 h for q.d. and 0, 2, 4, 6, 8, 10, and 12 h for b.i.d.). The availability of the new microemulsion formulation of CsA (Neoral) may streamline the endeavor, because with this formulation, trough levels show an improved correlation with AUC ( $r^2$ , 0.81 versus 0.50 with a standard nonmicroemulsion formulation) and achieve good estimates of full AUC with only a 2- and 6-h sampling during a 12-h dosing interval (11). The use of the new microemulsion formulation is associated with reduced variability in CsA kinetics, implying that single trough levels will be more consistent. With this formulation, CsA absorption is less dependent on bile acids and not affected by food intake (12). It is hoped that the greater reproducibility of CsA pharmacokinetic profiles when using the new microemulsion formulation (11,13) will facilitate dosage adjustment to compensate for inter- and intraindividual differences and will facilitate the incorporation of pharmacokinetic approaches into transplant care. The major practical limitation, however, for AUC monitoring is the necessity for blood collections to be made at precisely timed intervals after oral dosing.

So far, comparative studies on AUC versus trough-level monitoring have not consistently shown overall superiority of either method (9). Well-designed, preferably randomized prospective clinical trials, including the new microemulsion formulation and employing specific, well-validated assays to measure CsA, will help to resolve this issue. In such studies, assay specificity and precision must be documented. There is widespread consensus that at present, trough-concentration monitoring is the most appropriate and practical (Table 1).

#### FREQUENCY OF MONITORING

The frequency of blood CsA concentration monitoring should depend on the time elapsed since transplantation, intercurrent illnesses, and concomitant therapy with drugs affecting CsA metabolism. The immediate posttransplant period is characterized by unstable graft function, extreme inter- and

TABLE 1. Therapeutic ranges for CsA obtained from a survey of transplant centers during 1994/1995

Center [No.]	Analytic method	Dosing interval	Immuno-suppression protocol	Therapeutic ranges ( $\mu\text{g/L}$ )	Transplant type
University of Pennsylvania Medical Center, Philadelphia, PA, U.S.A. [1]	HPLC	b.i.d.	III	100–250 <3 mo 80–125 >3 mo	K
			III	200–300	L
			III	200–300 <12 mo	H
			III	100–150 >12 mo	
			III	250–350 <12 mo 200–300 >12 mo	Lu
Oklahoma Transplantation Institute, Oklahoma City, OK, U.S.A. [2]	mFPIA	b.i.d.	II	400–500 <6 mo 200–400 >6 mo	L
Georg-August-Universität, Göttingen, FRG [3]	EMIT	b.i.d.	III	150–200 <3 mo 100–150 >3 mo	K
			II + ALA	150–200 <3 mo 100–150 >3 mo	L
			IV	250–350 <3 mo 150–250 >3 mo	H
St. Christophers Hospital for Children, Philadelphia, PA, U.S.A. [4]	m $^{125}\text{I}$ -RIA	b.i.d., t.i.d.	III	100–200 <3 mo 75–150 >3 mo	K
			III; I, 12–18 mo	250–350 <3 mo 150–250 >3 mo	L
			III	250–350 <3 mo 100–200 >3 mo	H
University of Cincinnati Medical Center, Cincinnati, OH, U.S.A. [5]	mFPIA	b.i.d., t.i.d. in children <24 mo	IV	250–375 <6 mo 100–250 >6 mo	K & K-Panc
			IV	350–450 $\leq$ 1 mo 250–350 2–6 mo 170–240 >6 mo	L
			IV	300–420 <6 wks 180–300 6–12 wks 120–180 >12 wks	H
Universitäts Krankenhaus Eppendorf, Hamburg, FRG [6]	mFPIA	b.i.d.	II, III in some patients	200–250 <3 mo 150–250 >3 mo	L
Hospital for Sick Children, Toronto, ON, Canada [7]	HPLC	b.i.d.	III	175–225 <3 mo 150–175 3–12 mo 100–125 >12 mo	K
			III	300–400 <3 mo 250–300 3–12 mo 200–250 12–18 mo 80–200 >18 mo	L
			III	250–325 <6 mo 200–250 6–12 mo 150–200 >12 mo	H
University of California Los Angeles (UCLA) Medical Center, Los Angeles, CA, U.S.A. [8]	HPLC and pFPIA Pediatric K only. The higher concentrations pertain to pFPIA	b.i.d.	III	250–375 800–1,000 <1 mo 225–300 700–900 1–2 mo 200–250 500–750 2–3 mo 125–200 400–600 3–4 mo 100–175 350–500 4–6 mo 100–150 325–425 >1 year	Ped K

TABLE 1. Continued

Center [No.]	Analytic method	Dosing interval	Immuno-suppression protocol	Therapeutic ranges (µg/L)	Transplant type
	mFPIA and pFPIA. The higher concentrations pertain to pFPIA	b.i.d.	III	350-450	Adult K
			III	800-1,000 <3 mo 100-150 200-350 >3 mo	Adult L
			III	280-300 500-800 <3 mo 200-400 600-800 <3 mo 100-200 400-600 >3 mo	Adult H
St George's Hospital, The Medical School, London, U.K. [9]	m <sup>125</sup> I-RIA	b.i.d.	III Steroids stopped at 3 mo	300-350 <6 wk 200-250 6 wk-6 mo 150-200 6 mo-1 year 80-120 >1 year	H
Mayo Clinic, Rochester, MN, U.S.A. [10]	HPLC	b.i.d.	III	150-250 <2 wk 150-200 <2 mo 100-150 >4 mo	K, Panc
			III	350 <2 wk 250-350 <2 mo 150-250 <4 mo 100-150 >4 mo	L
			IV	250-350 2 wks-2 mo 75-125 >2 mo	H
Princess Alexandra Hospital, Brisbane, Australia [11]	HPLC	b.i.d.	III	120-200 <3 mo 100-160 >3 mo	K
			III <3 mo II >3 mo	250-300 <3 mo 200-250 3-12 mo 100-150 >12 mo	L
University of Texas Health Science Center, Medical Center, Houston, TX, U.S.A. [12]	mFPIA	Dosing based on pharmacokinetic studies to achieve steady-state conc.	II	550 <1 mo 500 2-3 mo 450 3-6 mo 400 6-12 mo 350 12-24 mo 300 >24 mo	K
	pFPIA		II	800-1,200 <1 mo 700-1,200 >1 mo	L
University of Virginia Medical Center, Charlottesville, VA, U.S.A. [13]	mFPIA	b.i.d.	III	150-250	K
			III	200-300	L
			III	150-250	H
			III	200-350 <2 mo 150-250 >3 mo	H-Lu
St. Johns Hospital & Medical Center, Detroit, Michigan, U.S.A. [14]	mFPIA	b.i.d.	IV	200-250 <1 mo 150-200 1-2 mo 100-150 2-3 mo 75-100 >3 mo	K
			IV	200	Panc
University of Alberta Hospitals, Edmonton, AL, Canada [15]	mFPIA	b.i.d.	III	300-400 <2 wks 250-300 2-4 wks 200-250 1-3 mo 150-200 3-6 mo 100-150 6-12 mo 100-125 >12 mo	K
			III	300-350 <30 days 250-350 30-60 days 250-300 60-90 days 200-250 90-180 days 175-225 180 days-1 year 150-175 >1 year	L
			III	350-500 <90 days 300-350 >90 days	H

TABLE 1. *Continued*

Center [No.]	Analytic method	Dosing interval	Immuno-suppression protocol	Therapeutic ranges ( $\mu\text{g/L}$ )	Transplant type
			III	400-500 <90 days 400-500 >90 days	H-Lu
Clin-Tox Associates, Germantown, TN, U.S.A. [16]	pFPIA Serum	b.i.d.	III	175-225 <30 days 125-175 30-90 days 75-125 >90 days	H
St. Vincent's Hospital, Darlinghurst, NSW, Australia [17]	mFPIA	b.i.d.	III	250-375 <6 mo 100-250 >6 mo	K
			III	350-450 >2 mo 300-400 2-3 mo 250-300 3-6 mo 200-300 6-12 mo 150-200 >12 mo	H, H-Lu
West Virginia University Hospitals, Morgantown, WV, U.S.A. [18]	mFPIA	b.i.d.	III	250-375 <6 mo 100-250 >6 mo	K
University of North Carolina Hospitals, Chapel Hill, NC, U.S.A. [19]	mFPIA	b.i.d.	III	~200 initial post Tx 150-200 >3 mo	K
			III	350 >6 mo 300 6-12 mo 200-250 <12 mo	H
			IV	400-500 <1 wk 250-350 2-3 wks 200-300 3-4 wks 180-280 >4 wks	L
			IV in children. Prednisone stopped after 3 mo	350 <6 mo 300 6-12 250 >12	H-Lu
			IV	400-500 <1 wk 250-350 >2 wks	Panc
Queen Elizabeth Hospital, Birmingham, U.K. [20]	mFPIA	b.i.d.	III	100-300	L
Huddinge Hospital, Stockholm, Sweden [21]	m <sup>125</sup> I-RIA	b.i.d.	III	250-350 <1 mo 200-300 1-2 mo 150-250 2-3 mo 70-150 >3 mo	K
			III	350-450 <9 days 250-300 9 days-3 mo 200-250 3-4 mo 150-200 >4 mo	L
			IV	300-400 <1 mo 200-300 1-2 mo 100-200 2-3 mo ~100 >3 mo	K-Panc, Panc
Neues Allgemeines Krankenhaus, Vienna, Austria [22]	mFPIA	b.i.d.	II	125-250 <3 mo 100-200 >3 mo	K
			II + ALA	125-250	L
Northwestern University Medical School, Chicago, IL, U.S.A. [23]	mFPIA	b.i.d.	III	250-400 <6 mo 250-300 >6 mo	K
	HPLC	b.i.d.	IV	200 <6 mo 200 <6 mo	L Panc
Univ.-Klinikum Rudolf Virchow, Berlin, FRG [24]	mFPIA	b.i.d.	IV	200-300 <4 wks 100-200 >4 wks	L
Academisch Ziekenhuis, Groningen, Holland [25]	HPLC	b.i.d.	III	200-250 <4 wks 100-150 >4 wks	L

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