Lung Deposition and Pharmacokinetics of Nebulized Cyclosporine in Lung Transplant Patients

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Abstract

Background: Inhaled cyclosporine (CsA) is being investigated as a prophylaxis for lung transplant rejection. Lung deposition and systemic exposure of nebulized CsA in lung transplant patients was evaluated as part of the Phase 3 cyclosporine inhalation solution (CIS) trial (CYCLIST).

Methods: Ten patients received 300 mg of CIS (62.5 mg/mL CsA in propylene glycol) admixed with 148 MBq of Tc-DTPA (technetium-99m bound to diethylenetriaminepentaacetic acid) administered using a Sidestream[®] disposable jet nebulizer. Deposition was assessed using a dual-headed gamma camera. Blood samples were collected over a 24-hr time period after aerosol dosing and analyzed for CsA levels. A pharmacokinetic analysis of the resulting blood concentration versus time profiles was performed.

Results: The average total deposited dose was 53.7 ± 12.7 mg. Average pulmonary dose was 31.8 ± 16.3 mg, and stomach dose averaged 15.5 ± 11.1 mg. Device performance was consistent, with breathing maneuvers influencing dose variation. Predose coaching with five of 10 patients reduced stomach deposition (22.6 ± 11.2 vs. 8.3 ± 5.2 mg; $p=0.03$). Blood concentrations declined quickly from a maximum of 372 ± 140 ng/mL to 15.3 ± 9.7 ng/mL at 24 hr post dose. Levels of AUC(0–24) [area under the concentration vs. time curve from 0 to 24 hr] averaged $1,493 \pm 746$ ng hr/mL. On a three times per week dose regimen, this represents <5% of the weekly systemic exposure of twice per day oral administration.

Conclusions: Substantial doses of CsA can be delivered to the lungs of lung transplant patients by inhaled aerosol. Systemic levels are small relative to typical oral CsA administration.

Key words: lung transplant, inhaled cyclosporine, aerosol deposition

Introduction

A NUMBER OF STUDIES have clinically evaluated the effects of inhaled cyclosporine (CsA) in lung transplant recipients.^(1–6) Early studies postulated that direct immunosuppressive treatment of the lungs would decrease the incidence of acute rejection events, which are a known risk factor for chronic rejection (bronchiolitis obliterans), the most significant cause of mortality after the first post-lung transplant year.^(7,8) However, the results of a single-center, placebo-controlled study with inhaled CsA published in 2006 showed distinct improvement in chronic rejection-free survival that was not associated with any change in acute rejection rate.⁽⁹⁾ The same formulation, cyclosporine inhalation solution (CIS), which contains 62.5 mg/mL CsA in propylene glycol, was

recently evaluated in a multicenter, randomized, controlled study (CYCLIST) to evaluate efficacy and safety in improving bronchiolitis obliterans syndrome (BOS)-free survival following lung transplantation. The dose regimen included three aerosol treatments per week on alternate days with one rest day. The aerosol delivery system and conditions of delivery were modestly different from those previously used.

The unique anatomy of lung transplant recipients and the potential for compromised respiratory function and lung disease necessitate a careful evaluation of pulmonary dosing. To evaluate delivery performance and systemic exposure after aerosol administration, 10 subjects in CYCLIST were asked to participate in a pharmacoscintigraphy substudy. In this study, pulmonary dosing and 24-hr pharmacokinetics were evaluated after a single 300-mg (nominal dose)

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treatment with CIS. Here we detail the techniques used and report on the results of the study.

Materials and Methods

Preclinical studies of Tc-DTPA with CsA

Deposition scintigraphy techniques rely on a relationship between active drug dose and radioactive counts from an externally detectable radiopharmaceutical. Here we have used technetium-99m bound to diethylenetriaminepentaacetic acid (Tc-DTPA) as a radiopharmaceutical deposition analogue. To demonstrate a robust relationship between CsA dose and radioactive counts across a range of aerosol sizes, we nebulized CIS with a small added volume of Tc-DTPA (148 MBq in <0.3 mL) and collected the aerosol using a Next Generation Impactor (NGI; MSP Corporation, Shoreview, MN). After 3 min of collection time, radioactivity was measured in each collection cup. The cups were then washed out using 50 mL of methanol, and the concentration of CsA was measured in each sample by high-performance liquid chromatography (HPLC). The percentage of collected CsA dose was then compared with the radioactivity in each aerosol size range. Five studies were performed and averaged. Calculations of mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were performed based on NGI data. Laser diffraction measurements of aerosol size were also performed using a Malvern Mastersizer S (Malvern Instruments, Worcestershire, UK). Measurements were made at 30-sec intervals over the first 3 min of operation and averaged. Two different nebulizers (same model) were used. Volume median diameters (VMD) are reported. GSD was calculated as VMD/84.1% volume diameter. Measurements were made in open-air conditions using a vacuum source to draw the aerosol through the measurement region.

Clinical materials

CIS was supplied in sterile glass vials at a concentration of 62.5 mg/mL in propylene glycol (DSM Pharmaceuticals, Parsippany, NJ). The minimum vial fill is 5.2 mL (325 mg of CsA) of which approximately 4.8 mL (300 mg of CsA) is dispensed into the nebulizer reservoir prior to dosing. Aerosol was generated using a Sidestream® disposable jet nebulizer (Philips-Respironics, Parsippany, NJ). The nebulizer "T" outlets were connected to a high-efficiency particulate air (HEPA) exhalation filter and a mouthpiece without an exhalation vent. A Mobilaire® compressor (Invacare, Elyria, OH) was used. This compressor provides adjustable air pressure and was set to 30 psig. Tc-DTPA was supplied in sterile saline volumes of <0.3 mL. This low volume of

aqueous solution is below the threshold of precipitation of CsA in the final mixture.

Study subjects

The study protocol was approved by the Institutional Review Boards of the University of Pittsburgh and of the Cleveland Clinic. Subjects in this substudy were already enrolled in the CYCLIST study—a Phase 3, multicenter, randomized, controlled study designed to evaluate the efficacy and safety of CIS in improving survival and preventing BOS when given prophylactically to lung transplant recipients in addition to their standard immunosuppressive regimen (NCT00755781). A total of 10 male subjects were consented and enrolled in the study (Table 1). By protocol, the immunosuppressive regimen of the patients did not include oral CsA, and all patients were required to be on a stable regimen of at least 250 mg of CIS for ≥3 months prior to the deposition study date. All subjects exhibited stable lung function at the time of investigation (Table 2).

Substudy design and procedures

All study procedures were carried out at the University of Pittsburgh Medical Center. The primary goal of the study was to define the pharmacokinetics of CIS. The secondary goal was to measure the total and regional deposition of CIS using scintigraphic procedures. Subjects were admitted to the Clinical Translational Research Center for a period of 36 hr during which all procedures were performed.

Prior to dosing, a physical exam was completed, the chest thickness was measured, a venous catheter was placed in a peripheral vein, and a 2-mL predose blood sample was collected. Subjects who used Chloraseptic® spray and/or albuterol (by metered dose inhaler) as part of their normal pre-CIS dosing routine also used this medication for the substudy. A full vial of CIS was dispensed into the nebulizer and admixed with 148 MBq (4 mCi) of Tc-DTPA (~0.3 mL). A HEPA exhalation filter collected excess aerosol generated by the nebulizer and any dose exhaled by the subject. This filter was replaced during dosing every 10 min or upon request by the patient. Stoppage for coughing or rest periods was allowed, and the additional dosing time was recorded. Patients inhaled the aerosol in a seated position, and posterior images were acquired throughout the dosing period. Immediately after dosing, patients were asked to lie down and both anterior and posterior gamma camera images were simultaneously collected. This was followed by a Tc-DTPA clearance measurement that included the sequential collection of posterior images over a 25-min period. Finally, a xenon-133 ventilation scan was completed. After the completion of aerosol administration, blood samples of 2 mL

TABLE 1. PATIENT CHARACTERISTICS

Subject #	1	2	3	4	5	6	7	8	9	10
Age (yr)	73	61	34	60	71	67	66	67	65	45
Weight (kg)	90.5	97.7	54.5	89.1	105.0	96.4	87.3	75.5	93.2	75.0
Time from transplant (days)	329	201	405	146	512	645	699	447	580	352
Transplant type	DLT	DLT	DLT	DLT	DLT	DLT	DLT	SLT	DLT	DLT

DLT, double-lung transplant; SLT, single-lung transplant.

TABLE 2. LUNG FUNCTION VALUES

Subject #	1	2	3	4	5	6	7	8	9	10
FEV1 (L) ^a	3.25	3.35	2.77	3.02	2.99	3.53	2.42	3.16	2.21	2.13
% of predicted	106.0	78.6	78.5	88.3	78.7	93.9	87.4	81.9	70.6	59.7
FEV1 max (L) during CYCLIST	3.72	3.35	2.79	3.29	2.99	4.05	2.42	3.22	2.22	2.17
FVC (L)	3.95	4.19	3.19	3.19	4.77	5.91	3.09	3.27	2.82	2.35
FEV1/FVC ratio (%)	82.3	80	86.8	94.7	62.7	59.7	78.3	96.6	78.4	90.6

CYCLIST is a randomized, controlled trial to evaluate efficacy and safety of inhaled CsA in improving BOS-free survival following lung transplantation.

^aAt the time of scintigraphic study.

were collected at 15, 30, 45, and 60 min and at 2, 4, 8, 12, and 24 hr, mixed in EDTA-coated tubes, transferred to cryovials, and stored at -20°C prior to shipping to a central laboratory (Covance Central Lab Services, Indianapolis, IN) for analysis of CsA concentrations. Subjects were domiciled in the research center overnight and were then discharged after the last sample was collected.

Predose coaching

The first five subjects evaluated were not given any specific instructions on how to breathe during aerosol delivery at the time of scintigraphy testing. However, these subjects did receive general instructions on nebulizer use at the time of randomization in the CYCLIST study, including one-on-one training by study staff, as well as a complementary instruction booklet and video. The last five subjects were given verbal reinforced instruction on breathing maneuvers immediately prior to scintigraphy dosing. The instructions included the use of slow inhalations with a brief pause ahead of exhalation. Subjects were also shown example images from other deposition studies to demonstrate the importance of proper breathing technique.

Analysis

The total drug dose delivered to the subject was determined using a scintigraphy mass balance technique. The radioactivity added to the nebulizer was measured prior to aerosol delivery using a nuclear medicine dose calibrator. After the dose was delivered, radioactivity was again assessed in the nebulizer, filters, and other delivery system components. Care was taken to ensure that the breathing circuit was "closed" during aerosol delivery. The total amount of radioactivity not recovered from the delivery system was assumed to be deposited in the subject. The total deposited CsA dose was then determined based on the percentage of radioactivity delivered to the subject and the starting CsA dose in the nebulizer. Emitted dose was calculated based on the percentage of radioactivity that remained in the nebulizer after delivery. Regional doses were then determined from anterior and posterior gamma camera images (256×256 pixels) collected after delivery. Images were exported as DICOM files and analyzed using ImageJ (NIH, Bethesda, MD). Lung perimeters were defined using equilibrium xenon gas images applied to Tc-DTPA deposition images. Deposited activity was divided into zones including mouth, trachea-esophagus, stomach, and right and left lung. Lung images were further divided into central and peripheral zones. The central zone was rectangular with one-

half the height and width of a rectangle outlining the whole lung image. It was positioned on the medial edge of the whole lung image at approximately mid-height. Counts from anterior and posterior images were background corrected and then combined in each zone using the geometric mean to account for differences in distance between the individual camera heads and the organs being measured. (A single camera head would underestimate dose in organs located further from its surface.) Central-to-peripheral dose ratio (C/P) is the ratio of technetium-99m counts in the central and peripheral zones without normalization by lung volume. The average of the left and right lungs is reported.

DTPA is an absorbable molecule, and different absorption rates may exist in different analysis zones.⁽¹⁰⁾ Correction for this effect was performed by measuring the clearance rate of DTPA from the individual analysis zones for 25 min after delivery. The relative clearance rates for each zone were determined and fit to exponential curves. The relative effect of absorption at the midpoint of the treatment time was then determined, and counts by zone were adjusted proportionally. A final adjustment was performed to correct for differences in attenuation based on measurements of chest thickness, as previously described.⁽¹¹⁾ The percentage of corrected counts by zone was applied to the total deposited dose, as previously determined through mass balance techniques, and CsA doses by zone were calculated.

Blood samples were processed for and analyzed by validated HPLC methodology using tandem mass spectrometry detection. Blood concentration versus time profiles for CsA were generated, and pharmacokinetic parameters including $T_{\max}$, $C_{\max}$, $t_{1/2}$, $\text{AUC}(0-24)$, and MRT_{ni} were calculated for each subject together with summary statistics. [$T_{\max}$ = time to maximum concentration, $C_{\max}$ = maximum blood concentration, $t_{1/2}$ = half-life, $\text{AUC}(0-24)$ = area under the concentration vs. time curve from 0 to 24 hr, MRT_{ni} = mean residence time (noninstantaneous).] These noncompartmental model estimates were generated using WinNonlin (Pharsight, Sunnyvale, CA).

Results

Preclinical studies of Tc-DTPA with CsA

Figure 1 shows percentage comparisons of CsA drug mass (as assessed by HPLC) and radioactivity associated with Tc-DTPA, by NGI stage. Figure 2 compares percentages of drug captured with percentages of radioactivity captured across all the stages. A strong linear relationship is demonstrated between radioactivity and CsA drug mass. The MMAD of the aerosol when calculated based on measurements of drug

FIG. 1. Comparing radioactivity and drug dose through NGI studies. Radioactivity is compared with drug mass within each aerosol size range after the nebulization of CsA solution for inhalation with a small amount of added Tc-DTPA. Results are means $\pm$ SD.

mass was $2.31 \mu\text{m}$ with a GSD of 2.00. Calculations based on radioactivity yielded MMAD of $2.44 \mu\text{m}$ with a GSD of 1.73. Laser diffraction instrument measurements of aerosol size yielded an average VMD measurement of $2.3 \mu\text{m}$ with a GSD of 2.5.

Deposition scintigraphy

All enrolled subjects completed both the scintigraphic and pharmacokinetic aspects of the study. The scintigraphy results are summarized in Table 3. The average run time of dosing (including stoppages) was 26.2 ± 6.7 min. One patient (#3) required multiple stoppages due to cough, resulting in a

FIG. 2. Demonstrating the linear relationship between CsA drug mass and radioactivity associated with Tc-DTPA. The correlation between radioactivity and drug mass provides the basis for the performance of deposition scintigraphy studies. Results are means $\pm$ SD.

total run time of 45 min. Dosing in patient #9 was adversely affected due to excessive salivation, resulting in precipitation of drug within the nebulizer reservoir. For this case, output as assessed by scintigraphy was approximately half of expected, although under such circumstances scintigraphy may not provide an accurate depiction of drug dose. The overall output from the delivery system was quite consistent, averaging 214.7 ± 35.2 mg of CsA, in spite of patient #9, whereas the average inhaled and deposited dose (total body dose) was 53.7 ± 12.7 mg across the subject group. Pulmonary deposition averaged 31.8 ± 16.3 mg, and stomach deposition averaged 15.5 ± 11.1 mg. The average C/P ratio in the group was 1.24 ± 0.68 . There was no significant change in lung dose due to predose coaching [34.3 ± 16.7 mg coached (#6–10) vs. 29.3 ± 17.4 mg uncoached (#1–5)] or in the C/P (1.19 vs. 1.27), but there was a significant drop in stomach levels (8.3 ± 5.2 vs. 22.6 ± 11.2 mg, $p=0.03$ by t test), suggesting that instruction may influence the dosing outcome (stomach + mouth, 10.4 ± 5.6 vs. 24.6 ± 12.1 mg, $p=0.04$). Figure 3 includes representative images from the deposition scintigraphy studies.

Pharmacokinetics

The CsA blood concentration versus time profiles indicate that a significant amount of CsA is absorbed rapidly with little time lag (Fig. 4), and peak levels drop below what would be considered *systemically* therapeutic within approximately an hour. Detectable levels in the circulation are present after 24 hr. The pharmacokinetic data for all patients are summarized in Table 4.

Dose correlations

Correlations between deposited doses, pulmonary function, and pharmacokinetic values are reported in Table 5. Deposited lung dose increased with lung capacity [forced vital capacity (FVC)] ($p=0.02$). Central lung dose and C/P ratio increased with FEV1%p [the percentage of predicted forced expiratory volume in 1 sec] ($p=0.05$, 0.01). The correlation between total deposited dose and AUC(0–24) approaches significance ($p=0.06$).

Discussion

The primary goal of the study was to define the pharmacokinetics of CIS. The secondary goal was to measure the total and regional deposition of CIS. Total CsA deposition here averaged 53.7 mg, and lung dose averaged 31.8 mg. These doses are higher than previously reported doses from other devices. Total dose is increased by 80% and 36% compared with doses found by Burckart *et al.*⁽¹²⁾ and Corcoran *et al.*,⁽¹³⁾ respectively. Pulmonary dose is increased by 18% and 6%, respectively.

Successful deposition of drug in the small airways is likely necessary to suppress chronic lung transplant rejection, which manifests as bronchiolitis obliterans, a fibrous obstruction of the membranous and respiratory bronchioles.⁽¹⁴⁾ These airways are large in number ($>4,000$) and small in diameter (~ 1 mm).^(15,16) Little knowledge exists on how to successfully target this zone; however, smaller aerosols are more likely to penetrate beyond large airways⁽¹⁷⁾ and breathing maneuvers⁽¹⁸⁾ may offer some utility. The MMAD of the CIS aerosol was $2.3 \mu\text{m}$, which is somewhat smaller

TABLE 3. DOSING INFORMATION FROM SCINTIGRAPHY STUDIES

Subject #	Run time (min) ^a	Emitted dose (mg)	Inhaled and deposited dose (mg)	Left lung (mg)	Right lung (mg)	Pulmonary dose (mg)	Stomach (mg)	T/E ^b (mg)	Mouth (mg)	C/P ^c
1	26	225.3	64.4	20.1	31.3	51.4	9.4	2.5	1.1	2.76
2	26	219.4	53.5	11.9	10.7	22.6	24.4	2.1	4.4	1.08
3	45	246.2	57.2	7.2	8.0	15.2	36.7	3.0	2.3	0.75
4	24	232.2	46.0	6.9	6.3	13.2	29.1	1.8	1.9	0.71
5	23	212.7	60.6	22.0	21.9	43.9	13.3	2.8	0.5	1.06
6	24	213.8	71.8	22.4	38.9	61.4	6.4	3.3	0.7	2.00
7	23	224.7	53.8	13.5	17.8	31.3	17.1	2.8	2.6	1.44
8	24	227.7	42.6	3.9 ^d	25.7	29.6	6.6	1.9	4.4	0.73
9	24	118.4	26.9	6.3	9.2	15.4	7.9	2.5	1.0	0.89
10	23	226.9	60.0	14.3	19.3	33.6	3.9	21.0	1.6	0.91
Average	26	214.7	53.7	12.9	18.9	31.8	15.5	4.4	2.1	1.23
SD	7	35.2	12.7	6.8	10.8	16.3	11.1	5.9	1.4	0.67

^aIncludes time for stoppages at subject request during dosing.

^bT/E, tracheal-esophageal region.

^cC/P, central-to-peripheral lung deposition ratio, average of left and right lungs.

^dSingle-lung transplant; left native lung.

than that of most aqueous aerosols generated by jet nebulizers and is likely a reflection of the physicochemical characteristics of the propylene glycol vehicle and the high operating pressure used to generate the aerosol (30 psig). Overall, 10.6% of the nebulizer fill dose (14.8% of the emitted dose) was deposited in the lungs—values typical for jet nebulizer therapy.^(19,20)

Deposited lung dose increased with FVC, indicating that higher lung doses are associated with larger lung volumes, likely due to increased total drug exposure. Previous studies have indicated an inverse relationship between FEV1 and central lung deposition.⁽²¹⁾ Here we see the opposite effect as central dosing increases with FEV1%p. In previous studies, decreased FEV1 was likely associated with large airway obstruction. Here it may simply indicate respiratory ability. Associations specifically with central lung dosing could be related to increased inhalation flow rates, or could be coincidence. Weak trends between both FEV1%p and FEV1 and lung dose are apparent when the data are examined carefully, and may indicate better dosing in healthier lungs.

Observations of oropharyngeal deposition and swallowing during early imaging studies prompted an enhancement to the procedure midway through the study. The first five patients who were evaluated were given no additional in-

struction beyond what was provided during the initial dose titration phase of CYCLIST. For the last five patients, the instructions for use were verbally reinforced immediately before dosing commenced. The outcome of these efforts was an observed drop in stomach deposition, indicating that improved breathing technique was indeed reducing oropharyngeal deposition. However, there were no statistically significant changes in total, pulmonary, or peripheral lung dose, C/P ratio, or AUC as a result of coaching in this small subject group, but trends toward improved dosing with coaching were seen.

Beyond coughing and some hoarseness, no other acute adverse effects were associated with CIS administration. However, the high initial lung doses do raise the question of whether the drug and/or vehicle will have a deleterious effect on lung tissue. *In vitro* culture studies using human airway epithelial cells have shown that 10 µg/mL concentrations of CsA cause increases in the release of lactate dehydrogenase and inflammatory cytokines and inhibition of cell growth.⁽²²⁾ However, the high lung concentrations post aerosol administration will decline rapidly, unlike those in cell culture, and aerosol studies carried out in beagle dogs administered CIS three times per week for 9 months at dose levels up to 12 times higher per kilogram than those received

FIG. 3. Deposition scintigraphy images from lung transplant recipients. (A) Subject with lowest pulmonary dose (13.2 mg). (B) Subject with highest pulmonary dose (61.3 mg). (C) A single-lung recipient [3.9 mg (native)/25.7 mg (transplant)]. All images are posterior.

FIG. 4. Blood concentration versus time profiles of CsA after inhalation. Time was assessed from the end of nebulized delivery. Results are means $\pm$ SD.

by human patients, demonstrated no macroscopic or histopathological changes to lung tissue.⁽²³⁾

The observations of drug reaching the stomach raise the possibility that oral absorption may contribute to the blood concentration versus time profiles after inhalation. No charcoal block was given prior to dosing, and therefore oral uptake cannot be ruled out. Visually, the profiles suggest that the impact of oral uptake is small, because peak concentrations were found 15–30 min post dose and declined afterwards. If oral absorption was significant, we would have expected skewed profiles in the 2–4-hr time frame. Mechanistically, unformulated CsA would be subjected to acid degradation within the stomach,⁽²⁴⁾ adding to the expected drug losses associated with gut wall and hepatic metabolism.⁽²⁵⁾

CsA inhalation is intended as a topical treatment of the lungs. Limited systemic exposure is desirable, because systemic CsA may contribute to nephrotoxicity and other undesirable side effects. In these studies, the average peak

TABLE 4. SUMMARY OF PHARMACOKINETIC DATA

Subject #	C_{max} (ng/mL)	T_{max} (hr)	AUC(0–24) (ng hr/mL)	MRT _{ni} (hr)	$t_{1/2}$ (hr)
1	522	0.25	1,971.7	5.3	10.4
2	259	0.25	992.5	5.6	7.8
3	453	0.25	1,765.1	5.5	12.6
4	206	0.25	714.9	5.4	17.4
5	226	0.5	960.7	6.0	10.9
6	537	0.25	2,028.4	5.2	9.3
7	338	0.25	1,292.2	5.7	8.4
8	476	0.25	1,536.3	4.8	10.4
9	199	0.25	607.8	6.0	12.6
10	501	0.25	3,059.0	6.8	6.9
Average	371.7	0.3	1,492.8	5.6	10.7
SD	140.0	0.1	745.9	0.6	3.0

C_{max} , maximum blood concentration; T_{max} , time to maximum concentration; AUC(0–24), area under the concentration vs. time curve from 0 to 24 hr; MRT_{ni}, mean residence time (noninstantaneous); $t_{1/2}$, half-life.

TABLE 5. CORRELATIONS BETWEEN DEPOSITED DOSE, PULMONARY FUNCTION, AND PHARMACOKINETICS

	FEV1(L)	FEV1%p	FVC (L)	AUC
Total deposited dose (mg)	0.19	0.27	0.07	0.06
Lung dose (mg)	0.19	0.16	0.02	0.17
Peripheral lung dose (mg)	0.40	0.86	0.06	0.18
Central lung dose (mg)	0.19	0.05	0.03	0.23
C/P ratio	0.25	0.01	0.14	0.40
Stomach dose (mg)	0.70	0.85	0.76	0.29
Stomach + mouth (mg)	0.66	0.88	0.71	0.28

p values based on linear regression are reported. Central lung dose and C/P ratio are positively correlated with FEV1%p. Lung dose and central lung dose are positively correlated with FVC.

FEV1%p, percentage of predicted 1-sec forced expiratory volume; C/P ratio, ratio of central-to-peripheral dose; AUC, area under the concentration vs. time curve from 0–24 hr (ng hr/mL).

systemic concentration (C_{max}) of inhaled CsA was 371.7 ng/mL with an average AUC(0–24) of 1,492.8 ng hr/mL. Burckart *et al.*⁽¹²⁾ reported C_{max} of 206.3 $\pm$ 89.6 ng/mL and AUC(0–24) of 1,033.9 $\pm$ 344.7 ng hr/mL. Previous studies of oral CsA administration in lung transplant recipients have reported peak levels of 1,710 $\pm$ 482 ng/mL, trough levels of 346 $\pm$ 112 ng/mL, and AUC(0–12) of 7,447 $\pm$ 1,870 ng hr/mL.⁽²⁶⁾ Total weekly exposure for inhaled CsA (three times per week) would be 4,479 ng hr/mL compared with weekly (twice per day) exposure of 104,258 ng hr/mL with oral CsA.⁽²⁶⁾ Thus, aerosol therapy would add only 4% to the typical cumulative weekly exposure of oral CsA therapy.

In summary, we have performed simultaneous deposition scintigraphy and pharmacokinetic studies of inhaled CsA in 10 lung transplant recipients participating in the Phase 3 CYCLIST studies. Peak systemic drug levels were similar to trough levels reported after oral administration, and the total systemic exposure associated with inhaled administration was a small fraction of the exposure associated with oral CsA administration. This study demonstrates the feasibility of inhaled drug delivery in lung transplant recipients. Although dosing was somewhat variable, delivery efficiencies typical for medical nebulizers were attained, and substantial pulmonary doses were achieved without excessive systemic exposure.

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Author Disclosure Statement

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