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PHARMACODYNAMICS, PHARMACOKINETICS, AND SAFETY OF MULTIPLE DOSES OF FTY720 IN STABLE RENAL TRANSPLANT PATIENTS: A MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, PHASE I STUDY

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Background. **FTY720, a novel immunomodulator, displays potent immunosuppressive activity in a variety of preclinical transplant models. This study examined the safety, pharmacodynamics, and pharmacokinetics of multiple doses of FTY720 in stable renal transplant patients.**

Methods. **This randomized, multicenter, double-blind, placebo-controlled, phase I study included adults who had been maintained on a regimen of cyclosporine A (CsA) microemulsion and prednisone (or its equivalent) for at least 1 year after renal transplantation. Patients received once-daily doses of 0.125, 0.25, 0.5, 1.0, 2.5, or 5.0 mg FTY720, or placebo for 28 days. After completion of study drug administration, the patients were monitored until day 56 by serial laboratory tests, clinical examinations, and recording of adverse events. The study includes 76 treatment courses (61 FTY720 and 15 placebo), with 65 patients enrolled once and 11 reenrolled.**

Results. **FTY720 doses greater than or equal to 1.0 mg/day produced a significant reduction in peripheral blood lymphocyte count by up to 85%, which reversed within 3 days after discontinuation of study medication. Compared with placebo-treated patients, FTY720 subjects did not show a major increase in adverse events or a change in renal function. Pharmacokinetic measurements revealed that FTY720 displayed linear relations of doses and concentrations over a wide range, but had no effect on CsA exposure.**

Conclusions. **At doses up to 5.0 mg/day for 28 days, stable renal transplant patients treated with FTY720 in combination with CsA and prednisone displayed a dose-dependent, reversible decline in peripheral blood lymphocytes without an enhanced incidence of collateral toxicities, except possibly bradycardia.**

FTY720 is a synthetic analogue of the natural compound myriocin, which is derived from the ascomycete *Isaria sinclairii* (*1*, *2*). This agent is unique from other immunosuppressants, because it does not impair T- or B-lymphocyte activation, cytokine synthesis, growth factor-driven proliferation, effector function, or memory cell generation by human cells in vitro (*3*) or in rodent models of alloimmunity (*4*) or viral infection (*5*). At clinically relevant concentrations, FTY720 appears to reduce the circulating peripheral blood lymphocyte pool not because of apoptosis (*6–9*), but rather by preferentially increasing cellular chemotaxis responses to homing more than inflammatory chemokines. This action accelerates lymphocyte migration to secondary lymphoid structures (*3*, *4*, *10–12*), which constitutively express high levels of homing chemokines (*13*). The sequestration prevents circulating lymphocytes from migrating to, becoming activated in, and subsequently destroying allografts (*14*).

The molecular mechanism of drug action has not yet been entirely clarified. After phosphorylation by sphingosine kinase, FTY720-phosphate binds to a subgroup of sphingosine-1-phosphate (S1P) G-protein receptors (formerly called EDG receptors)—$S1P_1$ (EDG1), $S1P_4$ (EDG6), and $S1P_5$ (EDG8)—triggering a cascade that enhances actin polymerization and augments cell motility (*15*, *16*). Because FTY720 displays synergistic immunosuppressive effects with cyclosporine A (CsA) (*17–21*), everolimus (*18*), tacrolimus (*22*), and sirolimus (*21*) in several animal transplant models, its unique mechanisms of action seem to complement those of other agents.

Administration of single oral doses of FTY720, ranging from 0.25 to 3.5 mg, to stable renal transplant patients maintained on a regimen of CsA and prednisone caused a dose-dependent, although transient, reduction in peripheral blood $CD4^+$ and $CD8^+$ T and B cells (*23*). At doses greater than 1.0 mg, the mean nadir counts were 30% to 60% below the baseline values. FTY720 was well tolerated except for the occurrence of bradycardic episodes, which were not associated with clinical symptoms or hypotension, and which resolved spontaneously without medical intervention. Pharmacokinetic analysis of whole blood concentrations after administration of a single dose revealed that FTY720 displays an extensive volume of distribution (1,116–1,737 L) and a moderate clearance rate (130–200 mL/min), resulting in a long terminal half-life ($t_{1/2}$), ranging from 89 to 157 hr. In addition, co-administration of single FTY720 doses did not affect blood concentrations of CsA.

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The present trial extended the single-exposure study by using multiple doses of FTY720 administered to stable renal transplant patients under treatment with CsA microemulsion and prednisone, seeking to evaluate the safety of the agent and its pharmacokinetics and pharmacodynamics, before the inception of trials to assess its therapeutic efficacy.

PATIENTS AND METHODS

Study Design

This multiple-dose study used a randomized, multicenter, double-blind, placebo-controlled design of time-lagged, ascending-dose, sequential-group entry. Each local committee for the protection of human subjects approved the trial, and patients signed informed consent documents before their participation.

Patient Population

Male and female renal transplant patients aged 18 to 65 years were enrolled if they were in stable clinical condition for at least 12 months after a first or second cadaveric or living-donor renal transplant. The study enrolled 65 patients for a first course: 11 were reenrolled for a second course to obtain 76 treatment courses (61 with FTY720 and 15 with placebo). All subjects had been receiving a constant dose of CsA microemulsion (Neoral; Novartis, Basel, Switzerland) and prednisone for at least 3 months before enrollment. Administration of azathioprine, mycophenolate mofetil, or cyclophosphamide was mandated to be discontinued at least 14 days before the first dose of study medication. Indeed, the majority of patients were treated at centers that do not routinely use purine synthesis antagonists for maintenance therapy. Furthermore, eligible patients were required to display acceptable laboratory values, vital signs, weight, and physical condition at screening and baseline, including a serum creatinine less than or equal to 3.0 mg/dL, an absolute (total) lymphocyte count greater than or equal to 1,200 cells/mm^3, and a pulse rate of 60 to 90 beats/min. Patients of childbearing potential were required to practice an approved method of birth control during the study and for 3 months after the last dose of study medication.

Exclusion criteria included graft rejection within 6 months of randomization; administration of other investigational medications, of trimethoprim-sulfamethoxazole, of ganciclovir, or of lymphocytolytic therapy to treat an acute rejection episode within 1 year of randomization; multiple organ transplants; clinically significant anemia; a history of significant coexistent liver disease, systemic infection, malignancy, immunocompromise, or active hepatitis; severe autonomic dysfunction; acute or chronic bronchospastic disease; heart disease or electrocardiographic abnormalities; any condition that significantly alters absorption, distribution, metabolism, or excretion of any pharmaceutic; illicit drug or alcohol abuse or tobacco product use within 12 months; or positivity for hepatitis B surface antigen. Because of the potential for FTY720-induced bradycardia, the protocol excluded the use of β-adrenergic blockers and diltiazem or verapamil, but not the dihydropyridine class of calcium channel blockers. Clonidine was prescribed for 12 of 61 (20%) patients in the FTY720 group and for 4 of 15 (27%) in the placebo arm.

Discontinuation of study medication was mandated in the event of an adverse reaction, protocol violation, withdrawal of consent, loss to follow-up, abnormalities in laboratory values or test procedure results, or administrative reason. Discontinuation was mandated when the therapeutic effect seemed to be excessive: if three consecutive measurements showed nadir (predose) total peripheral blood counts of less than 200 lymphocytes/mm^3 or less than 75 CD4$^+$ cells/mm^3.

Medication Administration

Patients were randomized in time-lagged groups on the basis of the oral dose of FTY720 (0.125, 0.25, 0.5, 1.0, 2.5, or 5.0 mg) or placebo. Study drug was ingested on days 1 through 28 in the morning simultaneously with CsA and at least 30 to 60 min before meals. Patients were only enrolled into the next higher dose of FTY720 after at least eight patients had received at least 21 days of therapy with a benign course in the opinion of the investigators, the Data Safety Monitoring Board, the U.S. Food and Drug Administration, and the sponsor. Eligible patients were allowed to reenroll into a higher dose cohort after a washout period of at least 3 months.

Throughout the study, CsA doses were selected to maintain whole blood morning 12-hr trough levels ($Cmin_{ss}$) between 100 and 200 ng/mL; the dose of prednisone was stipulated to be less than or equal to 15 mg/day. No reduction in CsA or prednisone doses was allowed; in the event of a clinically relevant biologic abnormality, the study medication was discontinued.

Assays

Blood concentrations of FTY720 were determined in a central laboratory (Novartis Drug Metabolism and Pharmacokinetics; Basel, Switzerland) using high-performance liquid chromatography coupled to mass spectrometry (Finnigan; Thermo Electron, Waltham, MA) with a quantification limit of 0.044 ng/mL. The method was validated by analysis of quality control spiked samples concurrently with the study samples. The mean accuracy and precision for nominal concentrations ranging from 0.057 to 10 ng/mL was 101.2% and 8.6%, respectively. Whole blood concentrations of CsA were measured at each center's local laboratory by a fluorescence polarization immunoassay using a parent compound-specific monoclonal antibody with a detection limit of 25 ng/mL (TD_X; Abbott Laboratories, North Chicago, IL).

Procedures

The study schedule included four phases: screening (days −60 to −1), baseline (day 0; before administration of study drug), treatment (days 1–28), and follow-up (days 29–56). In addition to screening and baseline visits, patients were examined on days 2, 3, and 4 and every 3 to 4 days thereafter through day 28 (the last day of study drug administration). Daily follow-up examinations were performed from day 29 to day 35 and every 3 to 4 days from day 38 to day 56. When the absolute lymphocyte count had not recovered to within 90% of the baseline value by day 56, the counts were monitored every 2 weeks thereafter for up to 3 months.

Laboratory evaluations included biochemistry, urinalysis, hematology, and flow cytometry enumeration of lymphocyte subsets bearing the surface markers CD3, CD4, CD8, CD14, CD16, CD20, CD45RO, and CD45RA. The baseline value was defined as the average of at least four and up to six measurements of the total lymphocyte count on day 0, namely, at 1, 2, 4, 6, and 12 hr on the day before administration of study medication. In addition, electrocardiogram, home pulse-blood pressure monitoring, pulmonary function tests, exercise oximetry, and ophthalmologic examinations were performed before and serially after drug administration.

FTY720 and CsA trough concentrations were monitored at all visits throughout the treatment and the follow-up courses. CsA pharmacokinetics were profiled by multiple samples drawn over a 12-hr interval on day 0 and on day 28. In addition to FTY720 pharmacokinetic profiles, including multiple blood samples on day 1 and day 28, trough FTY720 concentrations were measured on days 2, 3, 4, 7, 10, 14, 17, 21, and 24 and at each visit during the next 4 weeks after the day-28 dose.

Analyses

All randomized patients who received at least one dose of study medication and had at least one evaluation were included in the safety analyses. Patients who reentered the trial were treated as new subjects. Results were summarized by treatment group and by visit. An adverse event was defined as any undesirable medical event reported spontaneously by the patient or discovered by the investigator, regardless of whether it was attributed to the treatment.

Adverse events were monitored throughout the study; coded using the *Sandoz Medical Terminology Thesaurus*; and rated as mild, moderate, or severe. A serious adverse event was any event that was fatal; life-threatening; required or prolonged inpatient hospitalization; caused permanent disability; or was associated with cancer, congenital anomaly, overdose, graft loss, or an acute rejection episode. Severe adverse events were defined as symptoms that caused discomfort of such a severity that the patient ceased study medication treatment or required additional agents or hospitalization to control it.

Noncompartmental methods implemented in the WinNonlin ProVersion 3.1 computer program (Pharsight Corporation. Mountain View, CA) were used to estimate pharmacokinetic parameters, namely, the maximal concentration (C_{max}), the corresponding time to maximal concentration (t_{max}), the area under the concentration-time curve (AUC_{0-24h} calculated by the linear trapezoidal method), the oral clearance (CL) (calculated as the quotient of the AUC_{0-24h} and the dose on day 28), the elimination phase $t_{1/2}$, and the accumulation index (AUC_{day28}/AUC_{day1}). Dose proportionality was evaluated by the power model approach (*24*). The effect of FTY720 co-administration on CsA pharmacokinetics was evaluated using linear mixed-effect models (AUC_{0-12h} and C_{max}) and the Wilcoxon signed rank test (t_{max}).

RESULTS

Demographics

The demographic features, including doses of concomitant immunosuppressive medications, were similar between study groups (Table 1) and consistent with those of a renal transplant population. The most common concomitant medical conditions in the FTY720 versus placebo patients were hypertension (92% vs. 87%) and urinary system disorders (82% vs. 87%).

Pharmacodynamics

During day 1, all patients showed a decrease in the absolute lymphocyte count from the baseline value. During the first 24 hr, subjects treated with 0.125 or 0.25 mg FTY720 showed changes similar to patients treated with placebo. Although recipients administered 0.5 mg or 1.0 mg FTY720 showed more profound changes, they displayed recovery to the baseline value at 20 hr. However, members of the 2.5- and 5.0-mg FTY720 groups showed reductions in peripheral blood lymphocyte counts by 60% of baseline that persisted to the end of the day (data not shown).

Figure 1 reveals that throughout the 28-day treatment period, the morning absolute lymphocyte counts showed a dose-dependent decrease from baseline in all treatment groups compared with the increase in the placebo group. Lymphocyte counts were reduced by up to 85% in the 5.0-mg/day group, with sustained mean lymphocyte counts of 300 to 400 cells/mm^3. All dose groups showed a trend toward recovery within 3 days after study medication discontinuation. By day 56, lymphocyte counts were above baseline in the 0.125-mg group, within 10% of baseline in the 0.25- and 0.5-mg groups, and trending toward the baseline value in the remaining treatment groups. The patterns of both the dose-dependent decreases from baseline and the recoveries were similar for lymphocyte subsets bearing CD3, CD4, CD8, CD16, CD20, CD45RA, and CD45RO surface markers. No effects were observed on the number of peripheral blood granulocytes, monocytes, eosinophils, erythrocytes, or platelets.

Other Laboratory and Clinical Evaluations

The mean serum creatinine and blood urea nitrogen values remained stable and similar over time in all treatment groups. A greater proportion of placebo- than FTY720-treated patients displayed increases in total cholesterol to values greater than 275 mg/dL, namely, 23% versus 5%, respectively (P=not significant [NS]). In contrast, although the mean values were not different, the incidence of hypomagnesemia was reported to be numerically, although not significantly, higher among the FTY720 versus the placebo group. The lack of consistent effects of FTY720 on either the serum magnesium or serum creatinine suggested that the agent did not potentiate CsA-induced renal dysfunction (Table 2). Three patients (one each in the 0.5-mg FTY720, 5.0-mg FTY720, and placebo groups) experienced mild sinus bradycardia without other notable changes in electrocardiographic or vital signs. In all treatment groups, the mean heart rate and the oxygen saturation during cardiopulmo-

TABLE 1. Demographics and immunosuppressive therapy of enrolled patients[a]

Feature	FTY720 (n=61) (%)	Placebo (n=15) (%)
Age (yr)		
Mean±SD	47.4±11.2	42.5±11.8
Range	20–63	27–63
Male gender	35 (57.4)	9 (60.0)
Ethnicity		
White	34 (55.7)	5 (33.3)
African American	6 (9.8)	4 (26.7)
Asian	0	1 (6.7)
Other (primarily Hispanic)	21 (34.4)	5 (33.3)
Diabetes mellitus	24 (39)	5 (33.3)
Weight (kg)		
Mean±SD	80.7±13.5	74.4±15.8
Range	55.5–126.4	47.9–106.7
Cyclosporine A dose, mean±SD (mg/day)	243.8±91.3	213.3±105.1
Corticosteroid dose, mean±SD (mg/day)	9.6±13.4	7.7±2.9

[a] None of the differences was significant.

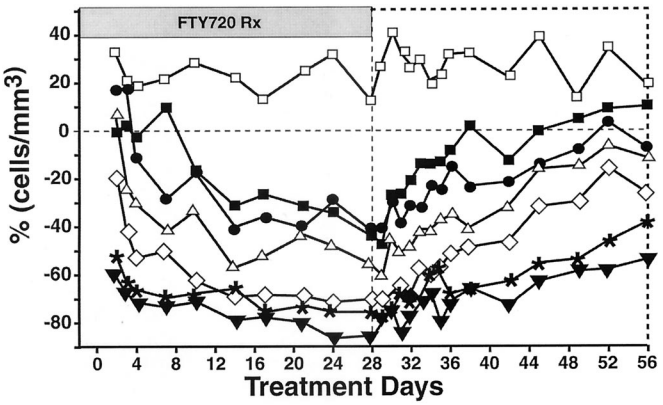

FIGURE 1. Impact of dose on the kinetics of percent change from baseline of the absolute lymphocyte count by study day during FTY720 treatment (28 days) and posttreatment (days 29–56) periods. (*open squares*) Placebo; (*filled squares*) 0.125 mg; (*filled circles*) 0.25 mg; (*open triangles*) 0.5 mg; (*open diamonds*) 1.0 mg; (*asterisks*) 2.5 mg; (*filled triangles*) 5.0 mg.

TABLE 2. Mean values of FTY720 pharmacokinetic parameters on day 28[a]

Dose (mg)	No.	Mean values (%CV)					Mean values (SD)	
		C_{max} (ng/mL)	t_{max}[b] (hr)	AUC_{0-24h} (ng/hr/mL)	CL (L/hr)	$t_{1/2}$[c] (hr)	Mg^{2+}	SCr
0.125	9	0.74 (79)	11.9 (0.6–22.2)	16.9 (21)	7.7 (20)	168 (136–281)	1.93 (0.2)	1.13 (0.5)
0.25	9	1.4 (42)	18.8 (11.4–24.5)	28.2 (52)	23.7 (190)	184 (141–252)	1.94 (0.3)	1.45 (0.5)
0.5	10	3.1 (39)	21.3 (0.3–24.2)	72.7 (29)	7.4 (28)	205 (145–528)	1.81 (0.3)	1.51 (0.4)
1.0	9	5.7 (50)	11.9 (1.3–22.7)	129.5 (48)	9.5 (47)	199 (133–399)	1.93 (0.2)	1.33 (0.5)
2.5	9	11.2 (49)	11.8 (10.0–24.0)	236.8 (45)	13.4 (65)	220 (134–526)	1.95 (0.2)	1.33 (0.4)
5.0	5	24.9 (54)	11.5 (11.3–12.1)	575.9 (31)	9.4 (33)	212 (157–338)	1.94 (0.3)	1.39 (0.3)
Placebo		NA	NA	NA	NA	NA	1.96 (0.3)	1.53 (0.5)

%CV, Percent coefficient of variation; CL, clearance; NA, not applicable; SCr, serum creatinine.
[a] $t_{1/2}$ was assessed during the terminal elimination phase (days 28–56).
[b] Median value (range).
[c] Harmonic mean (range).

nary exercise tests increased over time. No clinically significant treatment-related changes were noted in any group for one-second forced expiratory volume, forced vital capacity, or diffusion capacity for carbon monoxide.

Pharmacokinetics

FTY720 pharmacokinetic profiles were obtained from 51 patients (Table 2). The AUC_{0-24h} and C_{max} showed approximately linear relations to FTY720 dose over a wide range (Fig. 2), with 21% to 52% interindividual coefficients of variation of the AUC_{0-24h} (Table 2). The values of t_{max}, CL, and $t_{1/2}$ appeared to be dose independent. Across all dose groups, the mean $t_{1/2}$ was estimated to be approximately 200 hr. During 28 days of daily dosing, the long $t_{1/2}$ led to an approximately 10-fold drug accumulation on the basis of comparison of day-28 versus day-1 AUC values. There was no evidence of a drug-drug interaction between FTY720 and CsA (Fig. 3). Neither the rate (measured by C_{max} or t_{max}) nor the extent of CsA absorption (measured by AUC_{0-12h}) was affected by co-administration of various doses of FTY720 as documented by comparing pharmacokinetic profiles obtained on day 0 and day 28.

Adverse Events

Although more adverse events were reported among members of the FTY720 group than the placebo arm (88.5% vs. 73.3%, respectively), the difference was not significant. Table 3 shows the events reported in more than 10% of patients in each group. Both serious (9.8% vs. 20.0%, respectively; P=NS) and severe (6.6% vs. 20.0%, respectively; P=NS) events were experienced by a greater frequency of placebo- than FTY720-treated patients. Events attributed to the study drug were mostly mild or moderate in severity and tended to be more common among FTY720-treated patients. Only two patients treated with FTY720 experienced events that the investigators considered to be drug-related (i.e., fatigue-dyspnea and transiently elevated liver function tests).

TABLE 3. Adverse events occurring among more than 10% of patients

Adverse event	FTY720 (n=61) (%)	Placebo (n=15) (%)
Any adverse event	54 (88.5)	11 (73.3)
Any serious adverse event	6 (9.8)	3 (20.0)
Any severe adverse event	4 (6.6)	3 (20.0)
Lymphocytopenia	18 (29.5)	1 (6.7)
Coughing	9 (14.8)	1 (6.7)
Rhinitis	9 (14.8)	1 (6.7)
Urinary tract infection	7 (11.5)	1 (6.7)
Headache	6 (9.8)	4 (26.7)
Gastroenteritis	1 (1.6)	2 (13.3)
Increased blood urea nitrogen	1 (1.6)	2 (13.3)

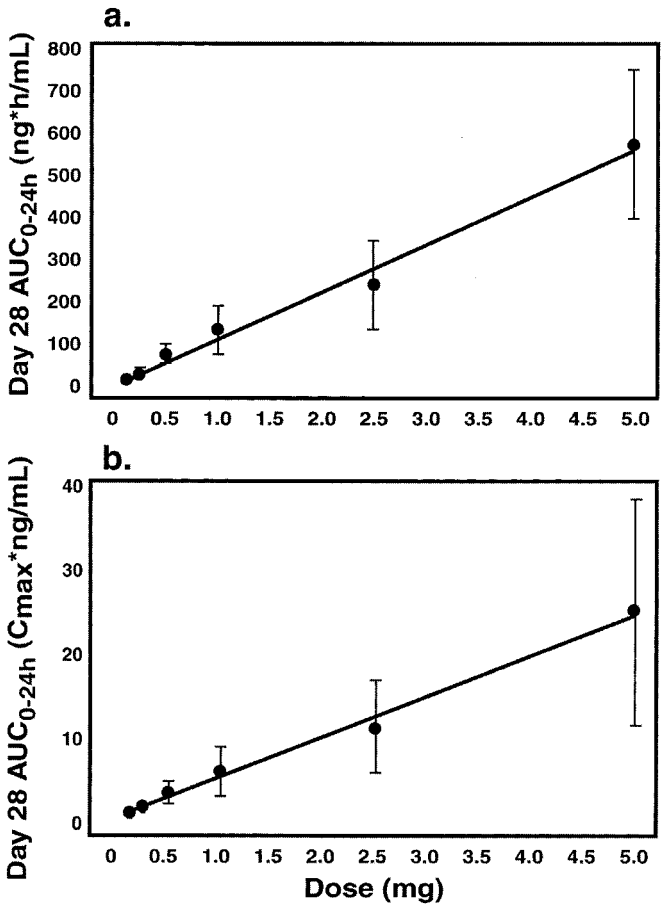

FIGURE 2. The relationship between FTY720 dose vs. AUC_{0-24h} (a) and C_{max} (b) on the last day (day 28) of drug administration. (*vertical lines*) Standard deviations (SD).

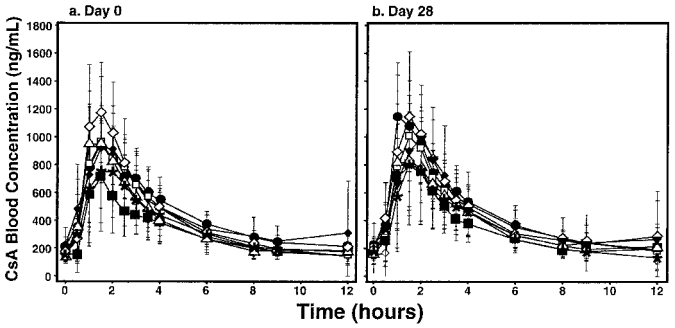

FIGURE 3. Mean (SD) of CsA blood concentrations vs. time before (a) and after (b) a 28-day course of FTY720 dosing. (*open squares*) Placebo; (*filled squares*) 0.125 mg; (*filled circles*) 0.25 mg; (*open triangles*) 0.5 mg; (*open diamonds*) 1.0 mg; (*asterisks*) 2.5 mg; (*filled triangles*) 5.0 mg.

Although bradycardia, which was defined as a decrease in pulse rate by 4 to 11 beats/min, had been reported as a frequent event among patients treated with FTY720 in a previous single-dose study (*23*), only 2 of 61 (3.27%) FTY720 patients and 1 of 15 (6.6%) placebo patients displayed this complication. One FTY720-treated patient experienced bradycardia on day 1 with recurrences on days 2 and 8. The second FTY720 patient displayed bradycardia on day 8. The placebo patient developed bradycardia on day 29.

Among the 11 patients (18% of the FTY720 group) who discontinued study medication prematurely, 9 met the protocol-defined criterion of a severe reduction in lymphocyte count. One of the other two subjects was discontinued because of an adverse event (dyspnea) and another because of elevated liver function tests on day 4, although the latter patient resumed therapy on day 13 and completed the 28-day course without recurrence or sequelae.

No deaths, episodes of rejection, or emergence of malignancy occurred in either group during the treatment and the follow-up phases. No patients who tested negative for cytomegalovirus antibody at screening converted to positive at day 29.

Approximately one third of all patients experienced infections; the incidences and patterns (bacterial vs. viral vs. fungal) were similar across all groups. Most infections (i.e., mild urinary or respiratory tract infections) were not serious (Table 4). Among these patients, two experienced severe infections: transplant pyelonephritis caused by multiple bacterial species on day 32 in a patient receiving 0.125 mg FTY720, and gastroenteritis on day 4 in a placebo-treated patient.

DISCUSSION

Multiple oral doses of FTY720 ranging from 0.125 to 5.0 mg produced a dose-dependent decrease in peripheral blood lymphocyte count during and delay in recovery over 3 days after discontinuation of FTY720 therapy despite its long $t_{1/2}$. At daily doses of 1.0 mg or higher, FTY720 produced approximately an 85% reduction in peripheral blood lymphocytes. All subsets of lymphocytes, but neither monocytes nor granulocytes, were affected by the drug.

FTY720 appeared to be well tolerated for up to 28 days in stable renal transplant patients maintained on CsA and prednisone. Comprehensive evaluations revealed no evidence of incremental safety risks compared with placebo-treated patients. All patients underwent the stipulated follow-up; however, 11 subjects discontinued study medication before completing the 28-day course primarily because of lymphopenia on the basis of an arbitrary definition of excessive pharmacodynamic effect. Severe and serious adverse events were reported two to three times more frequently in placebo- than in FTY720-treated patients.

The immunosuppressive effects of FTY720 were not associated with enhanced paralysis of nonspecific host responses. The incidence of infections was similar among patients in the treatment and placebo groups, consistent with a lack of alteration in primary or memory responses to bacterial and viral infectious challenges, an observation that confirms pre-

TABLE 4. Enumeration of serious adverse events in all groups

Age/gender	Dose	Serious adverse event	Day reported	Suspected relation to study medication
FTY720				
58/Male	0.125 mg	Pneumonia	21	No
50/Female	0.125 mg	Urinary tract infection	32	No
54/Female	0.125 mg	Fatigue	2	Yes
		Dyspnea	2	Yes
		Anxiety	2	Yes
		Palpitation	2	Yes
21/Female	0.25 mg	Fever	32	No
		Nausea	32	No
		Vomiting	32	No
		Diarrhea	32	No
50/Female	5.0 mg	Herpes zoster	7	No
51/Female	5.0 mg	γ-Glutamyl transferase increased	–1	Yes
		NPN increased	3	Yes
		Hepatic enzymes increased	3	Yes
Placebo				
47/Female	NA	Cerebrovascular disorder	24	No
63/Male	NA	Tachycardia supraventricular	37	No
30/Male	NA	Gastroenteritis	4	No

NPN, non-protein nitrogen.

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