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FTY720: Early Clinical Experience

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ABSTRACT

FTY720 is the first in a new class of immunomodulators—sphingosine 1-phosphate receptor (S1P-R) agonists. It is highly effective in prolonging allograft survival in preclinical models of transplantation. Furthermore, FTY720 acts synergistically with calcineurin inhibitors and proliferation inhibitors in these models, suggesting that use of FTY720 in combination with classical immunosuppressants may be a promising new option for transplant patients. Phase I studies conducted in stable renal transplant patients maintained on a cyclosporine (CsA)-based regimen have revealed a tolerable profile of FTY720 for transplant pharmacotherapy. The pharmacokinetics of FTY720 is characterized by linear dose-proportional exposure over a wide range of doses, only moderate interpatient variability, and a prolonged elimination half-life ($t_{1/2}$ 89 to 157 hours). These factors suggest that FTY720 can be administered according to a simple once-daily schedule, without the need for blood-level monitoring or dose titration. The pharmacodynamics of FTY720 in humans are characterized by a significant reduction in peripheral blood count by up to 85%. In contrast to the nonspecific myelosuppressive effects of other immunosuppressants, this effect of FTY720 is specific for lymphocytes, with no effect observed on monocytes or granulocytes. In combination with CsA, FTY720 was well tolerated following single or multiple dosing, without any evidence of additional toxicities, indicating that FTY720 may be useful in the future design of more effective and less toxic regimens for prevention of graft rejection.

CYCLOSPORINE (CsA) has made a substantial contribution to the prevention of acute rejection in human organ transplantation ever since its introduction into clinical practice. Development and improvement in other modes of rejection prophylaxis followed; nevertheless, chronic rejection, infection, and immunosuppressant drug toxicity remain the most common causes of morbidity and mortality in the transplant population.[1,2] Consequently, research has focused on the development of effective, yet less toxic, agents for preventing graft rejection.

FTY720 is a structural and functional analogue of the natural serum lipid sphingosine; hence, it is the first in a new class of immunomodulators—sphingosine 1-phosphate receptor (S1P-R) agonists. This agent has been shown to be effective in prolonging allograft survival in animal models of cardiac, renal, and hepatic transplantation.[3] Moreover, the unique mode of action of FTY720 is synergistic with classical immunosuppressive agents. Thus, this completely new mode of action with no overlapping toxicity with classical agents implies that FTY720 may provide an alternative for the future of transplant rejection prophylaxis.[4]

MECHANISM OF ACTION OF FTY720

The mode of action of FTY720 is distinct from any other drug approved or developed for use in solid-organ transplantation. After phosphorylation in vivo, FTY720 acts as a potent agonist at four S1P-Rs—a novel class of G-protein–coupled receptors.[5,6] Agonism at S1P-Rs by FTY720 reduces the recirculation of lymphocytes to blood and peripheral tissues,[7,8] including inflammatory lesions and graft sites.[9] FTY720 sequesters naive and activated $CD4^+$ and $CD8^+$ T cells and B cells from the blood into lymph nodes and Peyer's patches, without affecting their functional properties.[9–11] This lymphocyte sequestration may be mediated by accelerated homing into lymph nodes, or "trapping" of

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Table 1. Mean Values for Pharmacokinetic Parameters Following 28-Day Treatment With Multiple Doses of FTY720 in Stable Renal Transplant Patients

Dose (mg)	n	Mean Values (%CV)		$AUC_{0-24\ h}$ (ng*h/mL)	CL (L/h)	$t_{½}^{\dagger}$ (h)	Mean Values (SD)	
		C_{max} (ng/mL)	t_{max}* (h)				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)

Abbreviations: %CV, percent coefficient of variation; CL, clearance; NA, not applicable; SCr, serum creatinine.
$t_{½}$ was assessed during the terminal elimination phase (days 28 to 56).
*Median value (range).
†Harmonic value (range).
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lymphocytes in lymphatic tissues.[3] Importantly, FTY720 does not impair cellular or humoral immunity to systemic viral infection, and it does not affect T-cell activation, expansion/proliferation, or immunological memory in preclinical models.[8]

EFFICACY AND SAFETY OF FTY720 IN ANIMAL MODELS OF TRANSPLANTATION

When used alone, FTY720 has been shown to prolong allograft survival with remarkable potency in animal models of transplantation.[10–12] FTY720 has no antiproliferative activity at therapeutically relevant concentrations[10,13] and synergizes effectively with inhibitors of T-cell activation and proliferation to prevent acute rejection.[3] In combination with subtherapeutic concentrations of CsA, FTY720 has been shown to protect skin, heart, small bowel, liver, and kidney allografts in rats, dogs, and nonhuman primates.[14] Similar results have been observed when FTY720 has been used in combination with rapamycin,[15] RAD,[16] and tacrolimus.[17] In combination with CsA, FTY720 has also been shown, in a murine cardiac transplantation model, to prevent perivascular inflammation and allograft arteriosclerosis, which are markers of chronic rejection.[18]

In addition, FTY720 has shown no nephrotoxic or mutagenic activity in any of the in vitro or in vivo studies performed to date.[13] Furthermore, there was no evidence of infection in cynomolgus monkeys administered with extremely high doses of FTY720 of up to 10 mg/kg per day for a 52-week period.[13] FTY720 is extensively metabolized in the liver via cytochrome enzymes that are not involved in the metabolism of CsA, rapamycins, or tacrolimus, and thus drug-drug interactions between these agents when coadministered with FTY720 are unlikely.[13]

CLINICAL EXPERIENCE WITH FTY720 IN PHASE 1 TRIALS

The pharmacokinetics, pharmacodynamics, and safety of FTY720 have been investigated in two randomized, double-blind, placebo-controlled, phase I studies involving stable renal transplant patients (at least one-year posttransplantation) maintained on a CsA-based regimen.[19–21] The first study involving 20 patients was designed to evaluate ascending (0.25–3.5 mg), single oral doses of FTY720,[19,20] while the second examined the effects of multiple, once-daily doses (0.125–5.0 mg), given over a 28-day period (FTY720, n = 61; placebo, n = 15).[21]

Pharmacokinetics

The pharmacokinetics after single-dose administration of FTY720 to patients have been characterized by a prolonged absorption phase, with an elimination half-life ($t_{½}$) ranging from 89 to 157 hours, which was independent of dose.[19] Furthermore, the absorption phase was very long and wide, with a time to maximum plasma concentration (t_{max}) of 8 to 36 hours across subjects. Maximum plasma concentration (C_{max}) and area under the curve (AUC) were proportional to dose up to 3.5 mg, with low intersubject variability. Furthermore, FTY720 had an unusually high apparent volume of distribution (median 1407 L) and a relatively low apparent oral clearance (median, 158 mL/min). The long absorption phase of FTY720 in humans is consistent with the results of experiments with FTY720 in animal models; the absolute bioavailability of FTY720 in different animal species is high (60%–90%), with maximum blood concentrations achieved in 2 to 24 hours.[22,23]

The findings of the single-dose study have been confirmed by those of an analysis of the pharmacokinetics of FTY720 following multiple dosing.[21] In this latter study, steady-state pharmacokinetic parameters were determined for the blood concentration versus time values from the time of the last FTY720 dose (day 28) until the end of the follow-up period (day 56) (Table 1). Consistent with the long $t_{½}$ of FTY720, almost all subjects took about 4 weeks of daily dosing to reach steady-state concentrations (mean $t_{½}$ 200 hours). At steady state, the median t_{max} was about 8 hours and was similar for all doses. Again, C_{max} and AUC displayed linear kinetics over a wide range. Importantly, there was no evidence of a drug-drug interaction between FTY720 and CsA in this study, and CsA exposure appeared

unaffected by coadministration of FTY720 at any dose measured.[21]

The prolonged t½ of FTY720 implicates that the agent can be given once daily, with little fluctuation over the dosing interval at steady state. Furthermore, the low intersubject variability observed following administration of FTY720 indicates consistent absorption and disposition of the drug, which should allow for a simple, standardized dosing regimen for all subjects, without the need for blood-level monitoring or individualized dose titration.[19] The use of a pharmacodynamic loading dose of FTY720 is currently under evaluation for certain situations where rapid attainment of decreased lymphocyte count is required (eg, in the de novo transplant setting).[21]

Pharmacodynamics

Animal transplantation models have consistently shown that FTY720, administered at pharmacological doses, induces a decrease in lymphocyte count; this has been a prerequisite for efficacy in preclinical trials.[7,9,14,16,22] This pharmacodynamic effect of FTY720 has also been observed in studies in humans following single and multiple dosing.

Administration of a single dose of FTY720 (0.25–3.5 mg) to 20 stable renal transplant patients resulted in a transient decrease in lymphocyte count within 4 hours of administration in all subjects.[20] This pharmacodynamic effect of FTY720 exhibited nonlinear dose-dependence, with the most prolonged and intensive reduction in lymphocyte count being observed in the 3.5-mg group; the effect on lymphocyte count had returned to baseline within 24 to 72 hours in patients receiving 0.25 to 1.0 mg FTY720, but lasted more than 96 hours in those receiving 3.5 mg FTY720.[20] Administration of FTY720 affected both B and T cells, with the greatest effects being observed on $CD4^+$ and CD45RA+ naïve T cells, while NK cells, monocyte, and granulocyte counts were unaffected.[20]

A marked decline in peripheral lymphocytes has also been demonstrated following multiple doses of FTY720 (0.125–5.0 mg) in stable renal transplant patients.[21] Twenty-eight-day treatment with FTY720 at doses greater than 1.0 mg produced a sustained reduction of blood lymphocyte count of approximately 85% of baseline (Fig 1). After cessation of treatment, recovery was evident within 3 days after the last dose, with a trend toward complete recovery to baseline values in all dose groups at the end of the follow-up period (day 56). All doses of FTY720 appeared to affect to a similar degree all lymphocyte subsets tested: $CD3^+$ (pan-T cell), $CD4^+$ (T helper), $CD8^+$ (T suppressor), $CD45RA^+$ (T naïve), $CD45RO^+$ (T memory), $CD20^+$ (B cell), $CD16^+$ (natural killer). In contrast to that observed with immunosuppressive agents that display nonspecific myelosuppressive effects (eg, azathioprine, mycophenolate mofetil, sirolimus), multiple doses of FTY720 had no effect on blood granulocytes, monocytes, or eosinophils, and also had no effect on the number of erythrocytes or platelets.[21]

The predominant effect of FTY720 on $CD4^+$ and naïve T cells observed in these pharmacodynamic studies supports the potential enhancing effect of the drug on sequestration of these cells into lymph nodes and Peyer's patches.[9,14] Furthermore, the findings of these studies suggest that pharmacokinetics may not completely account for the pharmacodynamic response to FTY720. Consequently, pharmacodynamic monitoring, by measuring lymphocyte number, may also be a useful predictor of the response to FTY720 in future trials.[20]

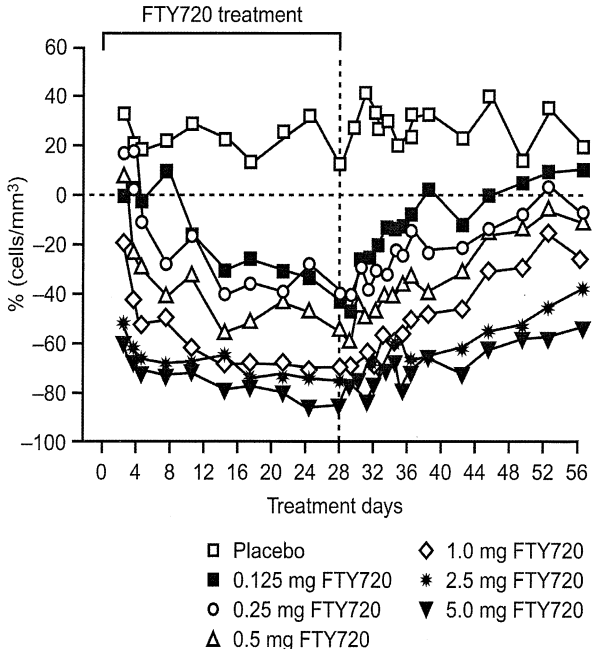

Fig 1. Impact of dose on the kinetics of percent change from baseline of the absolute lymphocyte count by study day during FTY720 treatment (28 days) and posttreatment (days 29–56) periods. Reproduced with permission by Kahan et al (Ref 21)

SAFETY AND TOLERABILITY

It has been found that FTY720 has a good tolerability profile in phase I trials, which may be related to the novel mode of action of the agent.[19–21] Use of FTY720 (0.25–3.5 mg) was well tolerated following single-dose administration, with no serious adverse events reported.[19] In the study by Budde et al,[19] 91% of FTY720-treated patients and 75% of placebo-treated patients experienced an adverse event. The most common adverse event reported was asymptomatic bradycardia, occurring in 10 FTY720-treated patients and none receiving placebo (Fig 2A). An increased frequency of reported bradycardia was observed in patients receiving higher doses of FTY720 (9 of 12 patients receiving ≥0.75 mg FTY720 vs 1 of 12 patients receiving ≤0.5 mg FTY720), mainly in patients with mild bradycardia (≤60 beats per minute [bpm]) at baseline. Heart rates reached a nadir about 4 to 8 hours after FTY720 dosing and lasted for up to 24 hours (Fig 2B). This transient reduction in heart rate on

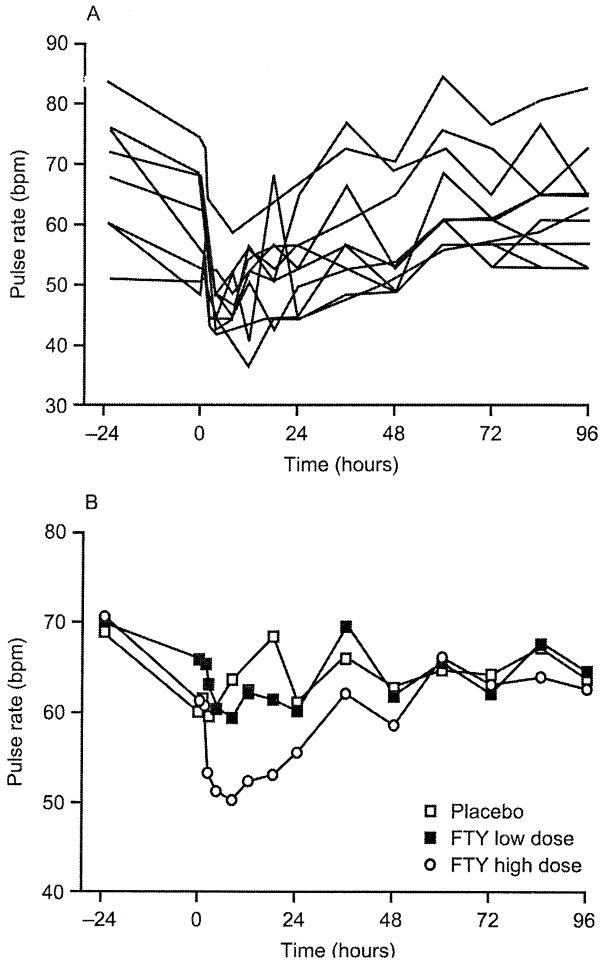

Fig 2. **(A)** Heart rate for 10 stable renal transplant patients with bradycardia receiving a single oral dose of FTY720 (0.25–3.5 mg). **(B)** Mean heart rate in placebo-treated subjects (n = 8) and in those receiving a low (0.25–0.5 mg; n = 12) or a high (0.75–3.5 mg; n = 12) dose of FTY720. Reproduced with permission by Budde et al.[19]

treatment initiation was asymptomatic, had normal blood pressure (BP) recordings at the time of nadir rate and required no clinical intervention in all cases; all patients recovered without sequelae. No additional organ toxicity was observed in this single-dose study, and no clinical signs or symptoms of pulmonary dysfunction were identified in any subject.

Following multiple dosing, FTY720 was equally well tolerated, with no significant difference noted between the incidences of adverse events in FTY720-treated patients compared with that seen in patients receiving placebo (88.5% vs 73.3%, respectively; Table 2).[21] Furthermore, serious and severe adverse events were reported more frequently in placebo-treated patients than in FTY720-treated patients (20.0% vs 9.8%, respectively, and 20.0% vs 6.6%). The incidences and patterns of infections (bacterial, viral and fungal) were similar in patients receiving multiple-dose FTY720 and in those receiving placebo, consistent with a lack of alteration of primary or memory responses to bacterial or viral infectious challenges, in accord with the findings of preclinical studies.[8,13] In addition, no deaths or episodes of rejection or emergence of malignancy were observed in this study, in either group, during the treatment or follow-up phases. Importantly, in contrast to the calcineurin inhibitors,[24,25] there is no evidence to date that FTY720 is associated with increased neurotoxicity or diabetogenic side effects,[21] suggesting that the agent may have an improved tolerability profile over classical immunosuppressants.

Table 2. Adverse Events Occurring in More Than 10% of Stable Renal Transplant Patients Following Multiple Doses of FTY720 (0.125–5 mg q.d.) or placebo for 28 days

Adverse Event, n (%)	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 (6.60)	3 (20.0)
Lymphocytopenia	18 (29.5)	1 (6.7)
Coughing	9 (14.5)	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 BUN	1 (1.6)	2 (13.3)

BUN, blood urea nitrogen.
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In contrast to the effects observed with FTY720 in the single-dose study, reduction in heart rate occurred infrequently in the multiple-dose study: in only 3.27% (2/61) of FTY720 patients and 6.6% (1/15) of placebo-treated patients.[21] This lower incidence may have been due to the exclusion of patients with resting pulses of less than 60 bpm and those receiving beta-adrenergic antagonists or calcium channel blockers at baseline.

Although the mechanism for this effect of FTY720 on heart rate is undergoing further investigations, it is reported that direct agonism of FTY720-P at S1P-R expressed in atrial myocytes of the heart is responsible.[3,26,27] Furthermore, the observation of a reduction on heart rate in the single-dose FTY720 study has led to the design of all subsequent trials with the drug to include close monitoring of heart rate in all patients. However, from trials completed to date, it appears that the transient effect of FTY720 on heart rate with treatment initiation is asymptomatic, self-limiting, and manageable and is not associated with any measurable increase in mortality or cardiac morbidity.

CONCLUSIONS

The availability of agents with different mechanisms of action for preventing graft rejection that can be combined safely will be essential for the future of organ transplantation if further improvements in outcomes posttransplant are

to be achieved. In contrast to classical immunosuppressants, FTY720 has no antiproliferative activity at therapeutic dosing and rather acts as a "stimulant immunomodulator," suggesting that this agent may be useful to augment the immunosuppressive actions of other drugs. Preclinical studies with FTY720 have demonstrated that the agent is highly effective in a wide range of animal models of transplantation.[13] Initial clinical studies with FTY720 suggest that this novel immunomodulator is also effective in human transplant recipients, producing a marked reduction in blood lymphocyte count following single and multiple dosing.[19–21] Furthermore, FTY720 in combination with CsA was well tolerated, with no significant safety issues. The novel mechanism of action of FTY720, its unique pharmacodynamic profile, and absence of additional toxicities when combined with CsA suggest that this agent may offer important benefits for the transplant setting. The results of ongoing studies investigating the ability of FTY720 to provide equivalent efficacy to classical immunosuppressive regimens in the prevention of acute rejection, without additional toxicity, are eagerly awaited.

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