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Treatment of Transplant Rejection

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Abstract

The first *Annual Review* in this issue of **Drugs of the Future** is dedicated to updated information on drugs for the treatment of transplant rejection. The following table lists 14 drugs under development in this area, some of which have been published in previous issues of the journal and others that have been launched for an indication other than that discussed in the review. Information on the following products is updated here: everolimus, FTY-720 and pentostatin.

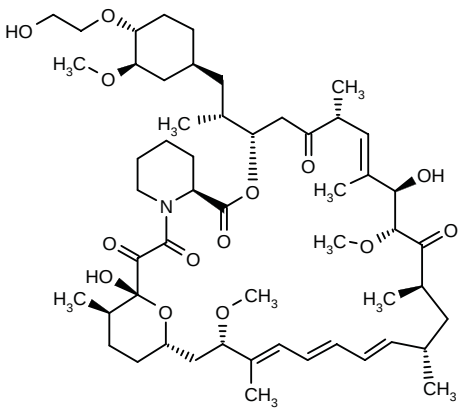
We would like to remind the readers that all of the information presented in this Review is available in electronic format in our drug discovery portal **Integrity**.

Annual Review 2002: Treatment of Transplant Rejection

Drug	Source	Indication	Phase
AGI-1096	AtheroGenics	Solid organ transplant rejection	I/II
AP-1903/Fas System	Ariad	Graft-*vs.*-host disease	II
APT-070C	AdProTech	Transplant rejection	I
Efalizumab[1]	Xoma	Kidney transplant rejection	I/II
Everolimus[1]	Novartis	Transplant rejection	III
FTY-720[1]	Mitsubishi Pharma/Novartis/Taito	Transplant rejection	II
Gavilimomab	Abgenix	Graft-*vs.*-host disease	III
HMR-1715	Aventis Pharma/Fujisawa	Transplant rejection	II
Inolimomab	Orphan Pharma International/Diaclone	Transplant rejection	II
ISAtx-247	Isotechnika	Renal transplant rejection	II
LEA29Y	Bristol-Myers Squibb/Novartis	Transplant rejection	II
Mycophenolic Acid Sodium Salt	Novartis	Transplant rejection	Prereg
Pentostatin[1,2]	SuperGen/Abbott	Graft-*vs.*-host disease	II/III
Visilizumab[3]	Protein Design Labs	Graft-*vs.*-host disease	II

Drugs in bold are covered in the review. [1]Previously published in Drugs of the Future. [2]Launched for another indication. [3]Monograph published in this issue.

Everolimus



Everolimus (SDZ-RAD, RAD-001, NVP-RAD-001, Certican™) is a potent proliferation inhibitor that targets primary causes of chronic rejection in organ transplant patients. Novartis has completed phase III trials with everolimus for the prevention of organ rejection in renal and heart transplant patients. In addition, the compound has shown positive results in preventing restenosis in animal models. Under a world-wide coexclusive license agreement, Guidant has obtained the rights to utilize everolimus in drug-eluting stents for the treatment of coronary and peripheral vascular diseases. Guidant hopes to initiate clinical trials of everolimus-eluting coronary stents later in 2002 (1).

The mechanisms by which sirolimus and everolimus enhance the negative effects of ciclosporin on mitochondrial metabolism were investigated and compared in rats. Coadministration of sirolimus and ciclosporin increased distribution of the agents into brain tissue, enhancing inhibition of mitochondrial glucose metabolism. The effects of ciclosporin were antagonized, however, by coadministration of everolimus, which decreased ciclosporin brain tissue concentrations. Everolimus also distributed into brain mitochondria (2).

Graft survival with everolimus alone or combined with FTY-720 was compared with that using ciclosporin treatment in a mouse cardiac allotransplantation model. Graft survival was increased with everolimus alone as compared to ciclosporin. Everolimus combined with FTY-720 was well tolerated with regard to weight gain and the lack of infection in the animals, and reduced the inflammatory response to a greater extent than everolimus monotherapy (3).

Immunosuppression with FTY-720 (0.3 mg/kg/day p.o.) plus basiliximab (10 mg i.v.) and everolimus (maintenance dose of 0.75 mg/kg s.c.) was evaluated in a non-human primate islet allotransplantation model. The immunosuppressive regimen studied demonstrated efficacy, and the procedures and immunosuppressants were well tolerated by the animals (4).

An open-label, single-dose, case-control study conducted in 8 subjects with moderate hepatic impairment and 8 healthy volunteers examined the pharmacokinetics of everolimus (2 mg p.o.). Subjects with liver impairment had a significant 53% reduction in apparent clearance as compared to healthy subjects (9.1 ± 3.1 l/h *vs.* 19.4 ± 5.8 l/h). As a result, AUC and $t/_{1/2}$ were 115 and 84% higher, respectively, in hepatically impaired subjects. Similar rates of absorption and rates of protein binding were observed for both groups. Everolimus AUC values and bilirubin levels were found to be significantly correlated, whereas a negative correlation was observed with albumin concentration. It was concluded that the everolimus dose should be halved in patients with mild or moderate hepatic impairment (5).

The pharmacokinetics of everolimus were evaluated in 24 healthy volunteers (given a single 2-mg dose) and 6 renal transplant patients (given a single 2.5-mg dose) when fasting and after a high-fat meal. A high-fat meal reduced the everolimus AUC, indicating that the drug should be administered regularly with or without food to obtain consistent levels of exposure (6).

The pharmacokinetics of everolimus were evaluated in 24 healthy volunteers who received everolimus 2 mg alone or with ciclosporin 175 mg or 300 mg. Both ciclosporin doses significantly increased everolimus exposure. Ciclosporin 175 mg significantly increased the everolimus C_{max} and increased the everolimus AUC to a significantly greater degree than the 300-mg dose (7).

The pharmacokinetics of the metabolites of everolimus and ciclosporin were determined in 3 renal transplant patients. Everolimus did not alter the pattern of ciclosporin metabolites when the agents were coadministered, and coadministration did not change the metabolic pattern of everolimus after steady-state concentrations were reached. However, the time to peak plasma levels of everolimus and its metabolites decreased (8).

In a pharmacokinetic and safety study, 26 *de novo* liver transplant recipients received everolimus in addition to ciclosporin and corticosteroids. Everolimus was well tolerated and was found to have a favorable absorption profile. In addition, everolimus treatment did not affect ciclosporin pharmacokinetics (9).

A 3-fold increase in everolimus levels in the presence of ciclosporin was confirmed in a study which compared early and delayed administration of ciclosporin in renal transplant patients already receiving everolimus (10).

Data on the possible interaction of everolimus with other drugs were presented for 16 renal transplant patients. Researchers reported that everolimus C_{min} values increased 3-fold when ciclosporin was administered concomitantly. It was concluded that no sudden changes in everolimus exposure are expected when everolimus is coadministered with ciclosporin (11).

In a randomized, open-label, 3-way crossover pharmacokinetic/pharmacodynamic study, 24 healthy volunteers were given single oral doses of everolimus 2 mg plus atorvastatin 20 mg or pravastatin 20 mg. A 14-day washout period separated the treatments. No clinically relevant pharmacokinetic changes were observed for any of the agents or for total HMG-CoA reductase inhibitors in plasma following coadministration of either of the statins and everolimus (12). Analysis of data from 2 pivotal trials demonstrated no clinical or pharmacokinetic interaction between statins and everolimus in renal transplant patients (13).

Lower rejection rates were reported for renal transplant patients receiving therapeutic drug monitoring (TDM)-based everolimus doses compared to patients receiving fixed everolimus doses (1.5 or 3.0 mg/day) or mycophenolate mofetil (2 g/day) (14). The role of TDM in renal transplant patients treated with everolimus and ciclosporin was analyzed in a study comparing the everolimus C_{min} values in renal transplant patients who received a fixed dose of the drug for 1 year and subsequent TDM-based doses for another year. TDM-based everolimus doses resulted in more stable C_{min} values and more C_{min} values in the therapeutic range than in patients receiving fixed everolimus doses, indicating that TDM may be a feasible option for everolimus dosing (15).

A multicenter, randomized, double-blind, crossover phase I study evaluated the pharmacokinetics and safety of everolimus in 20 stable lung and heart/lung transplant recipients, 8 of whom had cystic fibrosis. Everolimus was administered as single doses of 0.035 or 0.10 mg/kg with ciclosporin, steroids and azathioprine on day 1, with the alternate dose given on day 16. Everolimus was found to be well tolerated and safe in all patients and did not affect ciclosporin pharmacokinetics. Overall everolimus exposure was the same in patients with and without cystic fibrosis (16).

The impact of comedications and demographics on the pharmacokinetics of everolimus were investigated using blood samples collected in 2 multicenter, randomized, double-blind trials in 673 kidney transplant patients. Neither age, weight nor sex appeared to influence everolimus clearance, although clearance was 20% higher in black patients as compared to non-black patients. Inhibitors of CYP3A also reduced everolimus clearance (17).

A study reported that lung transplant patients show higher C_{min} values for everolimus than kidney transplant patients. It was also found that higher trough levels were associated with a greater incidence of hyperlipidemia and thrombocytopenia, and were also seen with coadministration of an azole antifungal agent and/or a macrolide antibiotic. Everolimus had no effect on ciclosporin pharmacokinetics in lung transplant patients (18).

The pharmacokinetic parameters measured for single-dose everolimus in stable pediatric liver allograft recipients were similar to those measured in adult patients when adjusted for body surface area. No drug-related adverse events were found, and everolimus had no apparent effect on ciclosporin pharmacokinetics in these patients (19).

The results of a 6-month study in pediatric *de novo* kidney allograft patients supported the use of body surface area-adjusted everolimus doses for these patients with therapeutic monitoring in order to individualize everolimus exposure (20).

A pharmacokinetic study in 634 adult patients revealed that everolimus exposure (0.75 and 1.5 mg b.i.d.) was dose-proportional and stable over the first 6 months after heart transplantation (21).

Investigators used data from 2 phase III studies comparing everolimus and mycophenolate mofetil (as part of triple immunosuppressive therapy with ciclosporin and steroids) to estimate the influence of lipid abnormalities on the 10-year probability of the occurrence of coronary heart disease events in renal transplant patients. No differences in predicted coronary heart disease event risk were seen between treatment groups based on variations in coronary risk factor profiles in these patients 1 year after transplant (22).

In a prospective, multicenter, randomized, controlled study, patients treated with everolimus showed less allograft vasculopathy at 1 year after cardiac transplant than patients treated with azathioprine. This suggested that everolimus could be used to prevent chronic rejection and thus contribute towards long-term survival of the patient (23). Results of this study and a number of the following trials are summarized in Table I.

An international, multicenter, 2-year study found that the incidences of efficacy failure and acute rejection were significantly lower in everolimus-treated cardiac transplant patients than in azathioprine-treated patients. Everolimus also resulted in lower viral infection rates compared to azathioprine, and the decrease in cytomegalovirus infection rates was statistically significant. Tolerance to everolimus was good (24).

Researchers utilized median effect analyses to compare the efficacy and toxicity of sirolimus and everolimus using data reported in large, multicenter, randomized trials. Overall, 977 patients received sirolimus and 695 everolimus as acute rejection prophylaxis. Greater efficacy was seen with sirolimus, which also demonstrated a 2-fold broader therapeutic window between immunosuppression and drug-induced toxicity (25).

A 1-year randomized, double-blind clinical trial of everolimus (0.5, 1 and 2 mg b.i.d. p.o.) in 101 patients with *de novo* kidney transplants showed dose-proportional pharmacokinetics and no influence of the agent on ciclosporin pharmacokinetics during the first year after organ transplantation. Steady state was reached on or before day 7, with a median accumulation ratio of 2.9 and peak trough fluctuations of approximately 90%. Drug absorption was delayed on day 1 as compared to steady state (median t_{max} = 3 h *vs.* 2 h). The mean C_{max} values ranged from 2.0 ng/ml to 9.8 ng/ml on day 1 and from 5.0 ng/ml to 21.9 ng/ml at steady state. The mean AUC values for doses of 0.5, 1 and 2 mg were 8, 28 and 56 ng·h/ml, respectively, after the first dose and 34, 81 and

Table I: Clinical studies of everolimus (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Heart transplant	Randomized, multicenter	Everolimus, 1.5 mg/d + Ciclosporin + Steroids x 1 y Everolimus, 3 mg/d + Ciclosporin + Steroids x 1 y Azathioprine 1-3 mg/kg/d + Ciclosporin + Steroids x 1 y	211	Everolimus treatment reduced the incidence and development of allograft vasculopathy, suggesting attenuation of chronic rejection, which may result in greater long-term survival after cardiac transplant	23
Heart transplant	Multicenter	Everolimus, 1.5 mg/d + Prednisone + Ciclosporin + Statins (n=209) Everolimus, 3 mg/d + Prednisone + Ciclosporin + Statins (n=211) Azathioprine, 1-3 mg/kg/d + Prednisone + Ciclosporin + Statins (n=214)	634	Everolimus was well tolerated and was more effective than azathioprine in decreasing acute rejection rate after heart transplant. The 3-mg dose was more effective but less safe than the 1.5-mg dose	24
Renal transplant	Randomized, double-blind, pooled/meta-analysis	Everolimus, 0.75 mg bid + Corticosteroids + Ciclosporin (trough 150-400 ng/ml x 1 mo → 100-300 ng/ml) Everolimus, 1.5 mg bid	695	Everolimus trough levels below 3 ng/ml were associated with a significantly greater risk of acute rejection. Adverse events seen with the highest trough level (15 ng/ml) were manageable	27
Heart transplant	Multicenter	Everolimus, 0.75 mg bid + Prednisone + Ciclosporin (trough levels 250-400 ng/ml in month 1 and 200-350 ng/ml thereafter) x 6 mo Everolimus, 1.5 mg bid + Prednisone + Ciclosporin (trough levels 250-400 ng/ml in month 1 and 200-350 ng/ml thereafter) x 6 mo Azathioprine	399	Everolimus up to C_{min} of 22 ng/ml was safe. Everolimus C_{min} was useful for distinguishing rejectors from non-rejectors in recipients of heart transplant. A putative lower end of the everolimus therapeutic range when combined with full-dose ciclosporin is 3 ng/ml. Thrombocytopenia was related to everolimus C_{min}	28
Renal transplant	Pooled/meta-analysis	Everolimus, 1.5 mg/d + Ciclosporin (tapered to 50-75 ng/ml) + Steroids Everolimus, 3.0 mg/d + Ciclosporin (tapered to 50-75 ng/ml) + Steroids Mycophenolate mofetil, 2 g/d + Ciclosporin (tapered to 50-75 ng/ml) + Steroids	453	Everolimus was safe and allowed a ciclosporin dose reduction associated with improvement in creatinine clearance in recipients of renal transplant	29 29
Renal transplant	Randomized	Everolimus, 1.5 mg/d + Ciclosporin + Steroids (n=194) Everolimus, 3.0 mg/d + Ciclosporin + Steroids (n=198) Mycophenolate mofetil, 2 g/d + Ciclosporin + Steroids (n=196)	588	Lower incidence of CMV infection in everolimus patients compared to mycophenolate mofetil-treated recipients of renal transplant	30
Renal transplant	Randomized, double-blind, multicenter	Everolimus, 1 mg/d + Ciclosporin + Corticosteroids x 6 mo Everolimus, 2 mg/d + Ciclosporin + Corticosteroids x 6 mo Everolimus, 4 mg/d + Ciclosporin + Corticosteroids x 6 mo	103	The 2- and 4-mg everolimus doses were more effective in lowering rates of acute rejection episodes than the 1-mg dose, with a significantly superior reduction in the severity of rejection	

164 ng·h/ml, respectively, at steady state. Regardless of the dose, AUC values showed a similar pattern over time. Inter- and intraindividual variability in dose-normalized AUC values was 85.4 and 40.8%, respectively; interindividual variability was not influenced by age (17-69 years), weight (49-106 kg), sex or ethnic group (white, non-white). Increasing everolimus AUC values were significantly correlated with an increased incidence of thrombocytopenia and a trend towards an increase in both hypertriglyceridemia and hypercholesterolemia. Clinically meaningful thrombocytopenia and leukopenia were uncommon; however, the hyperlipidemia seen required treatment. During coadministration with ciclosporin, the AUC and C_{min} for ciclosporin were similar throughout the study regardless of the everolimus dose (26).

Data from 2 randomized, double-blind phase III trials of everolimus in *de novo* kidney transplantation were analyzed to determine a therapeutic concentration range for the agent in this setting. It was found that trough levels below 3 ng/ml were associated with a significantly greater risk of acute rejection. No upper therapeutic concentration limit was identified, as the adverse events seen with the highest trough level (15 ng/ml) were manageable (27). The efficacy and safety of everolimus were

evaluated in a study in 399 cardiac transplant patients. Analysis of results indicated that a C_{min} of 3.4 ng/ml for everolimus distinguished rejectors from non-rejectors. The levels of hyperlipidemia found among everolimus-treated patients were not dose-limiting, and the overall incidence of everolimus-related thrombocytopenia was low (28).

A study conducted in maintenance renal transplant recipients treated with ciclosporin and everolimus reported that a decrease in the ciclosporin dose improved renal function, as indicated by improved creatinine clearance, without inducing any episodes of acute rejection (29).

A phase III study in 588 *de novo* renal transplant recipients found a lower incidence of cytomegalovirus (CMV) infection in everolimus-treated patients compared to mycophenolate mofetil-treated patients. This lower incidence was unrelated to the use of prophylaxis or the CMV status of donors and recipients, and the authors considered it to be especially relevant for the prevention of chronic graft rejection (30).

A multicenter, randomized, double-blind trial was conducted to compare everolimus (1, 2 or 4 mg/day) plus ciclosporin and corticosteroids in 103 *de novo* renal transplant recipients. After 6 months of therapy, it was found that the 2- and 4-mg doses of everolimus were associated with lower rates of acute rejection episodes than the 1-mg dose. The higher doses were also significantly superior in reducing the severity of rejection (31).

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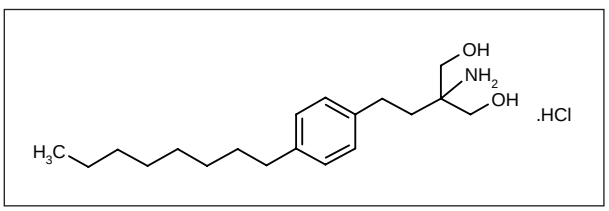
FTY-720



FTY-720 (Mitsubishi Pharma, Taito, Novartis) is a novel immunosuppressant which is currently undergoing phase II trials for organ transplantation. The compound represents a novel concept in immunosuppression, protecting the transplant against T-cells without affecting the host's ability to respond to antigens.

A new synthesis of FTY-720 has been reported: Condensation of 4-chlorobenzaldehyde (I) with octylzinc iodide (II) by means of Ni(0) gives 4-octylbenzaldehyde (III), which is treated with vinylmagnesium bromide (IV) to yield the allyl alcohol (V). Epoxidation of (V) with MCPBA affords the epoxide (VI), which is opened by means of $NaNO_2$ and $MgSO_4$ in refluxing methanol to provide 3-nitro-1-(4-octylphenyl)propane-1,2-diol (VII). Reaction of diol (VII) with trimethylsilyl chloride and NaI in acetonitrile gives 3-nitro-1-(4-octylphenyl)-1-propene (VIII), which is hydrogenated with H_2 over Pd/C in ethanol yielding the corresponding nitropropane derivative (IX). The bis-formylation of compound (IX) with aqueous HCHO in the presence of Amberlyst A-21 in dichloromethane affords 2-nitro-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol (X), which is finally reduced with H_2 over Ra-Ni to provide FTY-720 (1). Scheme 1.

Experiments *in vitro* and in mice shed light on the mechanism of action of FTY-720, which modulates lymphocyte traffic, causing sequestration of circulating lymphocytes into secondary lymphoid tissues (2).

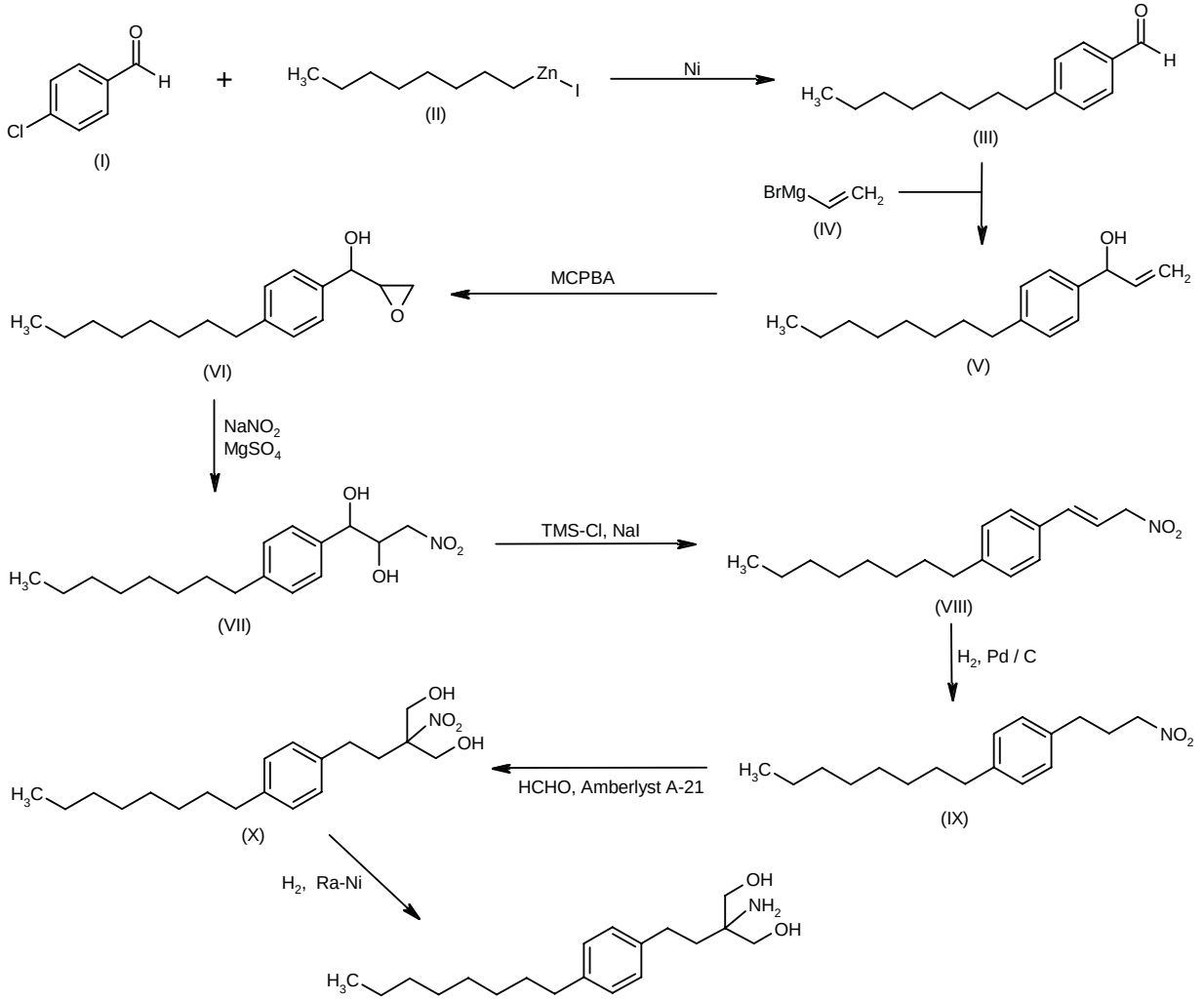
Graft survival with FTY-720 treatment alone was compared to that with FTY-720 plus ciclosporin in rat heart and skin graft models. In both models, combined ciclosporin/FTY-720 treatment lengthened graft survival; heart graft survival increased dose-dependently at FTY-720 doses of 0.01-1 mg/kg/day and skin graft survival was greatly extended at FTY-720 doses of 0.3 and 1 mg/kg (3).

The efficacy of oral FTY-720 (0.03-0.5 mg/kg/day for 21 days) alone and in combination with ciclosporin (20 mg/kg/day p.o. on days 7-20) or everolimus (0.5 mg/kg/day p.o. on days 7-20) was examined *in vivo* in cynomolgus monkeys. Treatment with 0.03-0.3 mg/kg FTY-720 was well tolerated; a dose of 0.5 mg/kg resulted in weight loss. FTY-720-treated animals showed a rapid reduction in white blood cell counts which was maximum after 3 days. Doses of 0.1 and 0.3 mg/kg/day FTY-720 decreased T- and B-lymphocyte counts by 80-90%. Although reductions in lymphocytes were not dose-dependent, blood concentrations of the agent were dose-proportional. FTY-720 exposure increased with combination ciclosporin treatment; this effect was not observed with everolimus coadministration. The reductions in peripheral lymphocytes were slightly increased with coadministration of everolimus but not with ciclosporin (4).

Researchers assessed the survival of islet grafts in diabetic mice treated with FTY-720. The median islet allograft survival was 11 days in untreated mice, while those receiving FTY-720 1 mg/kg for 50 days had a median islet allograft survival of 80 days. Islet xenograft (rat-to-mouse) survival was also significantly prolonged in FTY-720-treated animals. *In vitro*, FTY-720 stimulated insulin secretion in isolated islets under both physiological and hyperglycemic conditions (5).

A study using a rat renal transplantation model showed the efficacy of FTY-720 (0.05-3 mg/kg/day p.o.) in significantly and dose-dependently prolonging allograft survival. Rats treated with the agent at doses of 0.05, 0.1, 0.5, 1 and 3 mg/kg/day had mean allograft survival values of 12.2 ± 3.3, 11.2 ± 2.4, 13.6 ± 0.9, 14.6 ± 1.7 and 20.2 ± 0.8 days, respectively, as compared to 7.2 ± 0.4 days in untreated controls. Peripheral blood lymphocytes were significantly decreased in animals treated with 3 mg/kg/day and the percentage of IL-2 receptor-positive cells in allografts was significantly less (3.10 ± 0.86% *vs.* 6.34 ± 0.81% in untreated animals). No differences in the CD4/CD8 ratio of spleen cells and graft infiltrate were observed between treated and untreated animals (6).

Scheme 1: Synthesis of FTY-720



An *in vivo* study using H-Y antigen-sensitized female rats challenged with syngeneic male skin grafts showed that pretreatment with FTY-720 (10 mg/kg 4 weeks after sensitization) preserved immunological acquired memory. Sensitized animals pretreated with FTY-720 showed a restored ability to reject subsequent H-Y incompatible skin isografts (mean survival = 33.9 ± 11.9 days) as compared to untreated controls (mean survival = 300 days) (7).

A preclinical study conducted by Japanese researchers used female thymectomized rats sensitized with H-Y antigen to evaluate the effects of FTY-720 on naive and memory T-cells. Rats treated with FTY-720 rejected syngeneic male grafts, and the authors concluded that FTY-720 induced apoptotic cell death in naive T-cells instead of memory T-cells (8).

Graft survival with everolimus alone or combined with FTY-720 was compared with that using ciclosporin treatment in a mouse cardiac allotransplantation model. Graft survival was increased with everolimus alone as compared to ciclosporin. Everolimus combined with FTY-720 was well tolerated with regard to weight gain and the lack of infection in the animals and reduced the inflammatory response to a greater extent than everolimus monotherapy (9).

In a cynomolgus monkey kidney allotransplantation model, the combination of FTY-720 at 0.1 or 0.3 mg/kg/day and low doses of ciclosporin or everolimus improved graft survival. Triple therapy with FTY-720 0.1 mg/kg/day, ciclosporin 10 mg/kg/day and everolimus 0.25 mg/kg/day also led to an extension of rejection-free survival (10).

The effect of FTY-720 on heart grafts using the heterotopic F344-to-Lewis rat transplantation model was investigated. Compared to control rats, treatment with FTY-720 decreased the damage score and inflammatory cell infiltration in the blood vessels of the transplanted heart. The same authors used the tracheal graft stenosis

model to determine the time-dependency of the immunosuppressive effects induced by FTY-720 and found that the tracheal epithelium was preserved only when the rats were pretreated with FTY-720 from 3 days before transplantation. These results suggest that FTY-720 might be used in the treatment of chronic graft rejection (11).

An *in vivo* study using rats with heterotopic cardiac transplants reported that treatment with FTY-720 (2 mg/kg/day on days 3-9 posttransplantation) significantly delayed acute rejection. Allograft survival in treated animals was 30.5 ± 6.7 days as compared to 9 ± 1.9 days in untreated controls. Increasing the FTY-720 dose to 4 and 8 mg/kg/day (24.9 ± 7.5 and 21.5 ± 6.4 days, respectively) also resulted in significantly longer survival time as compared to controls. In addition, treated animals had less lymphocytic infiltration in allografts examined 7 days posttransplantation (12).

Immunosuppression with FTY-720 (0.3 mg/kg/day p.o.) plus basiliximab (10 mg i.v.) and everolimus (maintenance dose of 0.75 mg/kg s.c.) was evaluated in a nonhuman primate islet allotransplantation model. The immunosuppressive regimen studied demonstrated efficacy, and the procedures and immunosuppressants were well tolerated by the animals (13).

To further study the tolerance protocol using bone marrow transplantation with costimulation blockade, rats were given total body irradiation, bone marrow cell transplantation, the anti-CD154 MAb CTLA4Ig and either rapamycin 0.2 mg/kg/day on days 1-29, ciclosporin 20 mg/kg/day on days 1-29, methylprednisolone 20 mg/kg/day on days 1-11 and 10 mg/kg/day on days 12-29, FTY-720 0.5 mg/kg/day on days 1-29, mycophenolate mofetil 20 mg/kg/day on days 1-29 or tacrolimus 2 mg/kg/day on days 1-29. Rapamycin, methylprednisolone, FTY-720 and mycophenolate mofetil demonstrated potential for safe use in this protocol (14).

Investigators assessed the effect of FTY-720 on graft survival in a fully allogeneic rat model of orthotopic small bowel transplantation. While FTY-720 alone for 2 weeks after transplantation only slightly improved graft survival, the combination of FTY-720 and donor spleen cell injection 1 week before transplantation significantly prolonged graft survival (15).

In a canine model of nonmyeloablative allogeneic hematopoietic stem cell transplantation, administration of FTY-720 did not enhance engraftment, with 4 of 5 dogs rejecting their grafts within 11 weeks (16).

In order to study the migration pattern of T-cells, researchers injected *in vitro*-generated alloreactive T-cells expressing the reporter gene EGFP into rats that had received a kidney graft. The recipient rats were then treated with different immunosuppressive drugs. FTY-720 prolonged graft survival for 1 day and decreased the number of circulating blood lymphocytes, but did not reduce the accumulation of EGFP+ cells. Similar results were found with RIB5/2 therapy, whereas standard triple therapy with immunosuppressants reduced the number of EGFP+ T-cells infiltrating the graft. These results suggest that FTY-720 or RIB5/2 might be used as immunosuppressants when gene-engineered alloreactive T-cells are used to carry therapeutic proteins to the graft (17).

In a preclinical study, cells from 3 human and rat epithelial cell lines treated with ciclosporin showed morphological changes consisting of elongation and a higher number of pseudopodia. Treatment with FTY-720 prevented these morphological changes and, at concentrations higher than 5 μM, induced apoptosis of cancer cells treated with ciclosporin. It was concluded that combination treatment with FTY-720 and ciclosporin might reduce the incidence of cancer in transplant patients (18).

Treatment of human bladder cancer cells and murine renal cancer cells with FTY-720 (0, 0.1, 1, 5 and 10 μM) in combination with ciclosporin (1 μg/ml) blocked the morphological changes caused by ciclosporin alone, and high concentrations of FTY-720 induced cancer cell apoptosis (19).

Researchers investigated apoptotic signal transduction mediated by FTY-720, etoposide and anti-Fas antibody in the human Jurkat T-lymphoma cell line. All 3 agents cleaved caspases and the incidence of apoptotic cells induced by the compounds was reduced by pretreatment with a broad-spectrum caspase inhibitor (20).

An *in vitro* study using the human myelogenous leukemia HL-60 cell line, the human lymphoid Jurkat T-cell line transfected with human bcl-2 and cell-free systems examined the mechanism of FTY-720-induced apoptosis. Results showed that the agent first induces permeability transition to cause further apoptotic activity. Caspase 3 was required for FTY-720-induced apoptosis but caspase 1 was not involved. The agent directly affected mitochondrial activity before caspase activation, including a reduction in transmembrane mitochondrial potential and induction of cytochrome c release. Bcl-2 overexpression resulted in suppression of all apoptotic activity in both intact cells and cell-free systems. No direct effects of the agent were observed on isolated nuclei or cytosol (21).

FTY-720 induced apoptosis *in vitro* in 2 human bladder cancer cell lines (T24 and UMUC3) and inhibited tumor growth in mice with subcutaneous transplants of the same human bladder cancer cell lines (22).

In a mouse breast cancer cell line and in a mouse breast cancer model *in vivo*, FTY-720 demonstrated potent anticancer activity, inducing cancer cell apoptosis and markedly reducing tumor metastasis (23).

The effect of FTY-720 on renal recovery was investigated in a rat model of ischemia/reperfusion injury. At 0.3, 0.5 and 1 mg/kg, FTY-720 reduced mortality as a consequence of renal insufficiency compared with untreated controls. While in control animals acute tubular necrosis could be seen with light microscopy on the second day, few histological signs of ischemic injury were found in animals administered FTY-720 1 mg/kg (24).

The effect of FTY-720 on ischemia/reperfusion injury was investigated *in vitro* and in mice. *In vitro*, FTY-720 significantly decreased lymphocyte infiltration. Also, whereas none of the control animals with ischemia/reper-

Table II: Clinical studies of FTY-720 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Renal transplant	Randomized, double-blind, multicenter	FTY-720, 0.125 mg od + (Ciclosporin + Steroids) x 28 d FTY-720, 0.25 mg od + (Ciclosporin + Steroids) x 28 d FTY-720, 0.5 mg od + (Ciclosporin + Steroids) x 28 d FTY-720, 1.0 mg od + (Ciclosporin + Steroids) x 28 d FTY-720, 2.5 mg od + (Ciclosporin + Steroids) x 28 d FTY-720, 5.0 mg od + (Ciclosporin + Steroids) x 28 d Placebo + (Ciclosporin + Steroids)	76	FTY-720 was well tolerated and produced a significant, dose-dependent, reversible decrease in peripheral blood lymphocyte counts in renal transplant recipients	30
Renal transplant		FTY-720, 5 mg/d + Ciclosporin + Steroids (n=8) Tacrolimus + Basiliximab + Steroids (n=22)	30	FTY-720 decreased T-cell counts but did not compromise antiinfectious cell-mediated immune functionality in renal transplant recipients	33
Renal transplant	Open	FTY-720, 2.5 mg po od (after a loading dose of 5 mg) + Everolimus, 2 mg bid (after a loading dose of 4 mg; adjusted to trough levels of 4-8 ng/ml) + Corticosteroids	56	The regimen of FTY-720 plus everolimus and corticosteroids was safe and effective in the immunoprophylaxis of high-risk renal transplant recipients recipients	34
Renal transplant	Randomized	FTY-720, 0.25 mg od (after a loading dose of 1-4 mg) + Ciclosporin + Corticosteroids x 12 wk FTY-720, 0.5 mg od (after a loading dose of 1-4 mg) + Ciclosporin + Corticosteroids x 12 wk FTY-720, 1 mg od (after a loading dose of 1-4 mg) + Ciclosporin + Corticosteroids x 12 wk FTY-720, 2.5 mg od (after a loading dose of 1-4 mg) + Ciclosporin + Corticosteroids x 12 wk Mycophenolate mofetil, 2 g/d + Ciclosporin + Corticosteroids x 12 wk	155	FTY-720 trough blood concentration did not yield additional value to predict the incidence of rejection in renal transplant recipients	35
Renal transplant		Stable patients: FTY-720, 0.125 mg/d + Ciclosporin, 281 mg/d (mean) + Prednisone, 9.8 mg/d (mean) x 28 d FTY-720, 0.25 mg/d + Ciclosporin, 281 mg/d (mean) + Prednisone, 9.8 mg/d (mean) x 28 d FTY-720, 0.5 mg/d + Ciclosporin, 281 mg/d (mean) + Prednisone, 9.8 mg/d (mean) x 28 d FTY-720,1.0 mg/d + Ciclosporin, 281 mg/d (mean) + Prednisone, 9.8 mg/d (mean) x 28 d Ciclosporin, 281 mg/d (mean) + Prednisone, 9.8 mg/d (mean) x 28 d *De novo* patients: FTY-720, 2.5-5 mg/d + Ciclosporin, 331 mg/d (mean; full or reduced dose) + Prednisone, 14.4 mg/d (mean) x 28 d Control: Ciclosporin, 375 mg/d (mean) + Prednisone, 17 mg/d (mean)	101	FTY-720 improved hyperlipidemia after renal transplant	36

fusion injury survived over 48 h, 7 of 16 FTY-720-treated animals did (25).

FTY-720 inhibits lymphocyte infiltration into inflammatory and immune-reactive sites by decreasing circulating lymphocytes and promoting their homing, possibly via an interaction with a G-protein-coupled receptor. The therapeutic effects of the compound are under evaluation in a number of immune and autoimmune diseases, including spontaneous lupus nephritis in mice (26).

A study has been performed in a Lewis rat model of experimental autoimmune myasthenia gravis. Repeated oral administration following sensitization or a single

administration prior to acetylcholine receptor sensitization in these animals was associated with improvement in clinical disease severity and reduced serum anti-acetylcholine receptor titers (27).

The first study in humans with FTY-720 was a randomized, double-blind, placebo-controlled pharmacokinetic and pharmacodynamic investigation of single oral doses of 0.25-3.5 mg in 20 renal transplant patients. Among the findings were slow absorption for FTY-720 and a half-life of up to 5 days. The pharmacokinetics were linear and intersubject variability was low. Doses of 0.5-3.5 mg induced dose-dependent, reversible lymphopenia (28).

The metabolism of FTY-720 was evaluated using radiolabeled oral drug (1 mg) in 4 healthy volunteers. FTY-720 was extensively metabolized and essentially no intact drug was excreted in feces or urine. The two major biologically inactive metabolites were detected in urine (29).

A randomized, double-blind, placebo-controlled safety and pharmacodynamic study of FTY-720 was conducted in 76 renal transplant patients 1 year or more after surgery. In addition to ciclosporin and steroids, patients received FTY-720 0.125, 0.25, 0.5, 1, 2.5 or 5 mg or placebo once daily for 28 days. FTY-720 was well tolerated and safe, and significantly reduced peripheral blood lymphocyte counts in an apparently dose-dependent manner. No pharmacokinetic interaction with ciclosporin was seen (30). Results of this study and several others described below are summarized in Table II.

The interaction of FTY-720 and ciclosporin (Neoral®) was assessed in a study that included subjects with mild to moderate psoriasis, who were randomized to receive a single FTY-720 dose alone or in combination with Neoral®. No interaction was found between FTY-720 and Neoral®, as evidenced by the lack of changes in the AUC and C_{max} values of the drugs when administered alone or in combination. The data support the combined use of FTY-720 and Neoral® in current and future clinical trials without any dose adjustments (31).

The influence of FTY-720 on the frequency of human cytomegalovirus (HCMV)-specific T-cells in renal transplant patients has been evaluated. Conventional immunosuppressive therapy and a combination of FTY-720 and low doses of ciclosporin did not significantly modify the frequency of HCMV-specific T-cells, but patients treated with FTY-720 and a conventional dose of ciclosporin showed no HCMV-specific T-cell response. These results suggest that FTY-720 and ciclosporin have synergistic effects on memory T-cell responses (32).

Researchers found that treatment with FTY-720 significantly decreased the T-cell and B-cell counts in the blood of renal transplant patients compared to control patients receiving standard immunosuppressive therapy. Nevertheless, the memory T-cell response in FTY-720-treated patients was not different from that measured in control patients (33).

A study determined the effects of an immunosuppressive regimen of FTY-720, everolimus and corticosteroids on acute rejection, graft loss and death in renal transplant patients at high risk of delayed graft function. According to the authors, the new combination therapy provided an adequate immunoprophylaxis in this type of patients and resulted in few treatment-related adverse events (34).

The relationship between FTY-720 dose, exposure and efficacy was investigated in 155 renal transplant patients who received different doses of FTY-720 or mycophenolate mofetil plus ciclosporin and corticosteroids. The incidence of biopsy-defined rejection within each dosing group was found to be unrelated to systemic exposure to FTY-720, defined as the drug's trough levels in blood (35).

Improved lipid profiles have been found among stable renal transplant patients treated with FTY-720. Fasting cholesterol and triglyceride levels decreased after administration of FTY-720 for 28 days and increased nonsignificantly after discontinuation of treatment with FTY-720. Renal transplant patients treated with FTY-720 showed lower increases in cholesterol and triglyceride levels after transplantation than control patients treated with ciclosporin and prednisolone but not FTY-720. FTY-720 was associated with a significant improvement in hyperlipidemia after renal transplantation (36).

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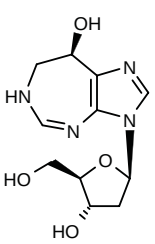
Pentostatin



Pentostatin (Nipent®) is an adenosine deaminase inhibitor which is currently marketed by SuperGen and Abbott for the treatment of hairy cell leukemia and is also undergoing phase II/III trials for the treatment of graft-*versus*-host disease.

Researchers have evaluated pentostatin in 10 patients with chronic graft-*versus*-host disease who had failed at least 1 immunosuppressive therapy. Pentostatin 4 mg/m^2 every 2 weeks was added to the patients'

Table III: Clinical studies of pentostatin (from Prous Science Integrity®)..

Indication	Design	Treatments	n	Conclusions	Ref.
Graft-*versus*-host disease	Open	Pentostatin, 4 mg/m^2 iv q/2 wk x 3 mo + Other therapy	10	Results suggest that pentostatin was well tolerated and demonstrated activity in this difficult-to-treat patient population	1
Allogeneic bone marrow transplantation therapy, graft-*versus*-host disease	Open	Pentostatin + Extracorporeal phototherapy + TBI → Ciclosporin + Methotrexate	39	Full donor engraftment was seen in the majority of patients, along with reduced rates of chronic and acute graft-*versus*-host disease	2
Allogeneic bone marrow transplantation therapy, renal cell carcinoma (stage unspecified)		Pentostatin, 1.75 mg/m^2 iv bolus q/2 d x 3 on d 7, 5 and 3 (n=3) Pentostatin, 2.5 mg/m^2 iv bolus q 2/d x 3 on d 7, 5 and 3 (n=3) Pentostatin, 3.25 mg/m^2 iv bolus q 2/d x 3 on d 7, 5 and 3 (n=3) Pentostatin, 4 mg/m^2 iv bolus q 2/d x 3 on d 7, 5 and 3 (n=3)	12	Conditioning with pentostatin was well tolerated and induced immunosuppression at even the lowest dose in patients undergoing allogeneic bone marrow transplantation	3
Allogeneic bone marrow transplantation therapy, bone marrow transplant, graft-*versus*-host disease	Open	Pentostatin + Extracorporeal phototherapy + TBI, 600 cGy → Ciclosporin + Methotrexate	42	The incidence of transplant-related complications was no different in patients under and over 45 years of age	4
Graft-*versus*-host disease, lymphoma	Open	Pentostatin + Mitoxantrone + Cytarabine	18	The conditioning regimen with pentostatin, mitoxantrone and cytarabine was safe and induced stepwise increases in donor chimerism, with no graft-*versus*-host disease seen at first immunosuppression and a complete response rate of 42% in these heavily pretreated refractory lymphoma patients	5

regimens; patients with improvement after 3 months had their other medications gradually discontinued. Pentostatin was well tolerated and demonstrated activity, with major and overall response rates of 50 and 60%, respectively (1). Results of this study and those that follow are summarized in Table III.

An allogeneic stem cell transplant conditioning regimen including extracorporeal phototherapy, pentostatin and TBI was evaluated in 39 patients at high risk for graft-*versus*-host disease. By day 30, 30 of 33 evaluable patients had full donor engraftment, and reduced rates of chronic and acute graft-*versus*-host disease were observed (2).

Investigators conducted a phase I/II dose-escalation study of pentostatin as a single-agent preparatory regimen for 12 patients undergoing allogeneic peripheral blood progenitor cell transplantation for metastatic kidney cancer. Three patients each received pentostatin 1.75, 2.5, 3.25 or 4 mg/m^2 i.v. every other day for 3 doses before transplantation. Conditioning with pentostatin was well tolerated and induced immunosuppression even at the lowest dose (3).

The effect of age on the outcome of allogeneic bone marrow transplantation was investigated in a study of a pentostatin-based preparative regimen. Patients (n=42) received extracorporeal phototherapy, pentostatin and 600 cGy TBI, followed by ciclosporin and methotrexate. The incidence of transplant-related complications was not different between patients under 45 and those over 45 years of age (4).

A conditioning regimen for stem cell transplant including mitoxantrone, cytarabine and pentostatin was evaluated in 18 patients with refractory lymphoma. The results indicated that the regimen was safe and induced stepwise increases in donor chimerism, with no graft-*versus*-host disease seen at first immunosuppression (5).

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