transplantation
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FTY-720 A PROMISING IMMUNOSUPPRESSANT IN NEW MILLENNIUM

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ABSTRACT

FTY-720 is a synthetic myriocin analogue derived from culture filtrates of Isaria sinclairii. Its mechanism of action was not understood till recently. It has been found to reduce peripheral T- B cell repertoire while increasing their number in lymph nodes and Payer's patches. This redirected "Homing" is thought to be a result of chemokine receptor modification by FTY 720 on lymphocytes.

FTY-720 is a sphyngosine 1-phosphate (S 1P) receptor agonist. S 1-P receptor agonists restrict egress of lymphocytes from lymphoid organs where they have been sequestered following administration of FTY-720. There is suppression of lymphocyte infiltration in to the allograft and prolonged lymphocytopenia although immunologic memory is not impaired and granulocyte number and function are not affected.

In phase II clinical trial, 2.5 mg dose of FTY-720 in combination with Cyclosporin (CsA) was as effective and safe as standard CyA/ MMF combination regimen and 5 mg dose permitted a safe reduction in CyA dose within 48 hours of the first dose. Up to 25 % patients developed reversible bradycardia without hemodynamic compromise. Phase III studies are in progress and their results will determine the place of this promising immunnosuppressant in clinical transplantation.

INTRODUCTION

Allograft tolerance is the ultimate dream of all transplanters. A search for newer and safer immunosuppressants or immunomodulators will continue till that dream is realized. Table 1 shows important landmarks in immunosuppressive therapy. FTY-720 can be considered an immunosuppressant of the new millennium, with distinct and novel mechanism of action.

Table 1 shows various milestones in immunosuppressive therapy in allograft transplantation.

1955 – 60	Radiation
1950 – 61	Mercaptopurine
1962	Azathioprine
1963	Azathioprine + Prednisone
1965	Polyclonal Antibodies
1976	Cyclosporine
1980-2000	Monoclonal antibodies
1990-2000	Tacrolimus
	Mycophenolate Mofetil, Sirolimus
2005	FTY - 720

Table 1 Milestones in Immunosuppression

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BIOCHEMICAL PROPERTIES OF FTY-720

FTY- 720 is a structural and functional analogue of the natural serous liquid sphingosine. Thus it belongs to a new class of immunodulators; sphingosine-1-phosphate receptor (S1 P-R) agonists. Its chemical structure is shown in figure-1. Its biochemical structure is known as 2-Amino (2-C2-[octyl-pheny] ethyl)-1-3 propenediol hydrochloride) of myricion. It was derived from culture filtrates of the fungus Isaria sinclairii, an ascomycetes mycelial member of fungi imperfecti characterized by asexual spore phases[1].

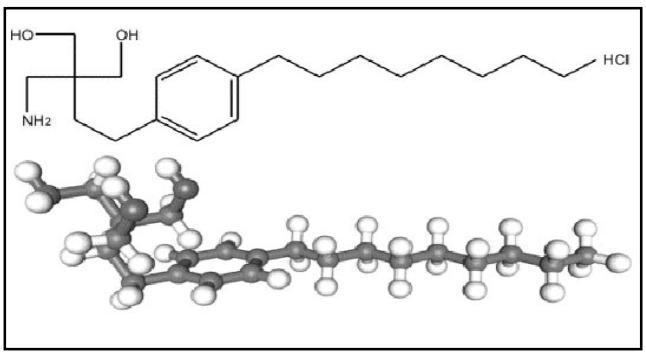

Figure 1 Biochemical Structure of FTY-720

MECHANISM OF ACTION

After phosphorylation in vivo FTY-720 acts as a potent agonist at four S1P-RS, a novel class of G-protein coupled receptors. Agonist at S1P-RS by FTY-720 reduces the recirculation of lymphocytes to blood and peripheral tissues including inflammatory lesions and allograft sites. FTY-720 sequesters naïve and activated $CD4^+/CD8^+$ T cells and B cells from blood in to lymph nodes and Payer's patches without affecting their functional properties. The lymphocyte sequestration may be mediated by accelerated homing in to FTY-720 mediated lymphocytes sequestration during microvascular passage lymph nodes or trapping of lymphocytes in lymphatic tissues[2]. FTY-720 does not impair cellular or humoral immunity to systemic viral infection or cancer cells and it does not affect T-cell activation, expansion/proliferation or immunological memory. Its mechanism of action is shown in figure 2.

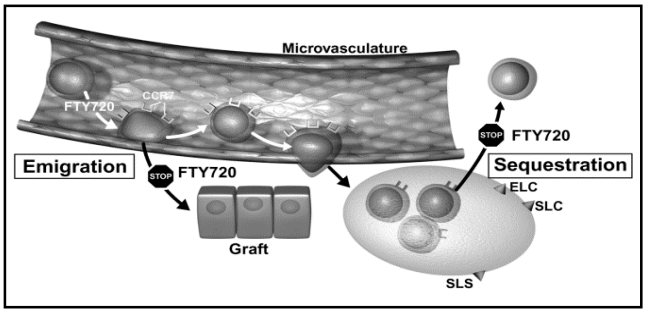

Figure 2 Mechanism of Action of FTY-720

PHASE I CLINICAL TRIAL

Two phase I clinical studies were carried out in stable renal transplant patients (at least 1 year post-transplant) maintained on CyA micro-emulsion based regimen. In these studies FTY-720 showed dose-dependant reversible reduction in peripheral blood lymphocyte count up to 80 % baseline, confirming findings of pre-clinical studies. FTY-720 was found to have excellent tolerability profile[3].

The most notable adverse event reported was a transient and asymptomatic reduction in heart rate associated with first dose of the agent in about 25 % of patients. The pathogenesis has been depicted in figure 3. The most significant observation was lack of evidence for drug-interaction between FTY-720 and CyA.

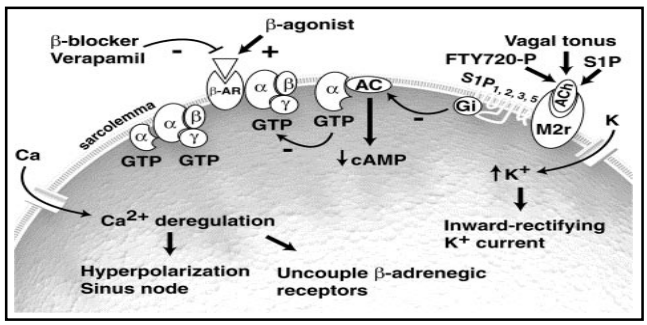

Figure 3 Mechanism of Sinus Bradycardia by FTY 720

PHASE II CLINICAL TRIAL

Phase I clinical trials with FTY-720 were conducted in stable renal transplant patients, phase II clinical trials sought to confirm the findings of the studies in recent renal transplant recipients. It was a multi-centre, randomized open-label, active controlled, dose finding study designed to assess pharmacokinetics and safety in immediate (renal)

posttransplant period. It compared efficacy and safety of 4 doses of FTY-720, (0.25/ 0.5/ 1.0/ 2.5 mg /day) to MMF, 2.0 gm/day in combination with micro-emulsified CyA and corticosteroids as shown in table 2. It showed that there was clear relationship between with FTY-720 dose, exposure and efficiency. FTY-720, 2.5 mg with CyA was as effective in preventing acute rejection as MMF[4].

Treatment	Number of Evaluable Patients	Biopsy-Proven AcuteRejection n(%)
FTY720 1 mg first dose, 0.25 mg/d	39	8 (20.5)
FTY720 2 mg first dose, 0.5 mg/d	37	13 (35.1)
FTY720 4 mg first dose, 1.0. mg/d	20	4 (20.0)
FTY720 2 mg first dose, 2.5 mg/d	28	1 (3.6)
MMF 2 mg/d	35	5 (14.3)

Table 2 Biopsy-Proven Acute Rejections

Biopsy proven acute rejection in de-novo renal transplant recipients : Interim analysis of 159 patients who had completed at least 30 days of treatment (data from Tedesco-Silva et al), is mentioned in table 2.

FTY-720 was found to have long half life of 210 hours, thus reducing its requirement to a single daily dose. It is soluble in water and ethanol making it effective orally. It seems to be metabolized primarily by hepatic cytochrome P4504F system. Its metabolites are immunologically not effective.

Co-variates like age, gender, race, body weight and indices of hepatic and renal dysfunction had no significant effect on FTY-720 clearance. It was also not affected by blood sugar level. FTY-720 eliminates the requirement of its blood levels.

PHASE III CLINICAL TRIAL

Phase III multi-center double blind trial is in progress at present and results will determine its place in clinical transplantation[5].

CONCLUSION

FTY-720 may be considered a promising immunosuppressant of the new millennium with novel structure and mode of action of 'homing' of lymphocytes. It has no detrimental effects on other blood components or on opportunistic infections and cancer phase I and II clinical trials have established its efficacy and safety in transplantation while ongoing phase III clinical trial will determine the place of this immuno modulator in clinical transplantation.

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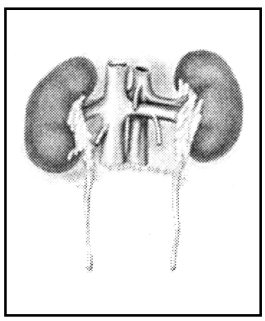
Renal Transplantation



The first human renal transplantation was done in 1936 by Voronoy in the Ukraine in a patient with mercury poisoning. In the early 1950s, two groups, one in Paris and the other in Boston, simultaneously restarted human kidney transplantation. The French surgeons used no immunosuppression but Hume in Boston used low dose steroids for immunosuppression. Although hardly a success, these results gave impetus to further human studies and fully successful transplants, first between identical twins and then between unrelated subjects using cadaveric donor kidneys.

Hume DM, Merrill JP, Miller BF, Thorn GW., J Clin Invest 1955; 34: 327.