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SIROLIMUS AS MAGIC BULLET FOR mTOR INHIBITOR IMMUNOSUPPRESSANT

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ABSTRACT

Sirolimus blocks certain white blood cells that can reject foreign tissues and organs. It also blocks a protein that is involved in cell division. It is a type of antibiotic, a type of immunosuppressant, and a type of serine/threonine kinase inhibitor. Sirolimus was previously called rapamycin. Sirolimus inhibits T-lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production.

KEYWORDS: Rapamycin, Interleukin, T-lymphocyte, Macrolide, Immunosuppressive, Lymphangioleiomyomatosis, mTOR.

Preamble: Rapamycin, marketed under the name sirolimus, is a macrolide compound with immunosuppressive functions and was first isolated from samples brought back from Easter Island by a microbiologist called Georges Nógrády. Suren Sehgal at Ayerst Research Laboratories, Montreal, where rapamycin was isolated in 1972. Intuitively one would have thought that an immunosuppressive compound would prevent an immune response against tumor cells and therefore would not be a likely anticancer drug.[1]

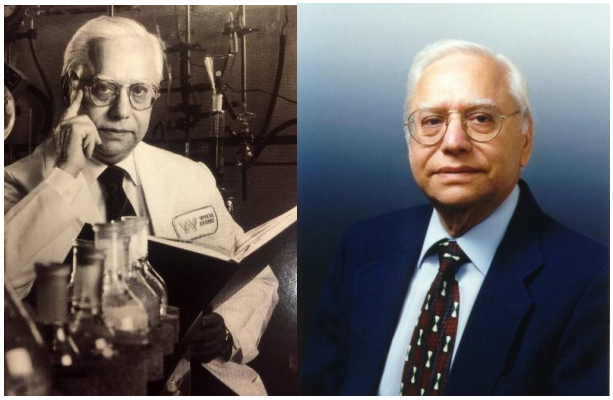

Figure-1: Georges Nógrády & Suren Sehgal; sirolimus project scientists of lymphangioleiomyomatosis.

Sirolimus [CAS: 53123-88-9] is an mTOR inhibitor immunosuppressant used to prevent organ transplant rejections, treat lymphangioleiomyomatosis, and treat adults with perivascular epithelioid cell tumors. The mammalian target of rapamycin (mTOR), also referred to as the mechanistic target of rapamycin, and sometimes called FK506-binding protein 12-rapamycin-associated protein 1 (FRAP1), is a kinase that in humans is encoded by the MTOR gene. mTOR is a member of the phosphatidylinositol 3-kinase-related kinase family of protein kinases. mTOR links with other proteins and serves as a core component of two distinct protein complexes, mTOR complex 1 and mTOR complex 2, which regulate different cellular processes. In particular, as a core component of both complexes, mTOR functions as a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, autophagy, and transcription.

As a core component of mTORC2, mTOR also functions as a tyrosine protein kinase that promotes the activation of insulin receptors and insulin-like growth factor 1 receptors. mTORC2 has also been implicated in the control and maintenance of the actin cytoskeleton. Lymphangioleiomyomatosis (LAM) is a lung disease caused by the abnormal growth of smooth muscle cells, especially in the lungs and lymphatic system. This abnormal growth leads to the formation of holes or cysts in the lung.[2]

Background: Sirolimus [(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E, 30S,32S,35R)-1,18-dihydroxy-12-{(2R)-1-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-2-propanyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo[30.3.1.0~4,9~]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentone], also known as rapamycin, is a macro cyclic lactone antibiotic produced by bacteria *Streptomyces hygroscopicus*, which was isolated from the soil of the Vai Atari region of Rapa Nui (Easter Island). It was first isolated and identified as an antifungal agent with potent anticandida activity; however, after its potent antitumor and immunosuppressive activities were later discovered, it was extensively investigated as an immunosuppressive and antitumor agent. Its primary mechanism of action is the inhibition of the mammalian target of rapamycin (mTOR), which is a serine/threonine-specific protein kinase that regulates cell growth, proliferation, and survival. mTOR is an important therapeutic target for various diseases, as it was shown to regulate longevity and maintain normal glucose homeostasis. Targeting mTOR received more attention especially in cancer, as mTOR signaling pathways are constitutively activated in many types of human cancer.[3]

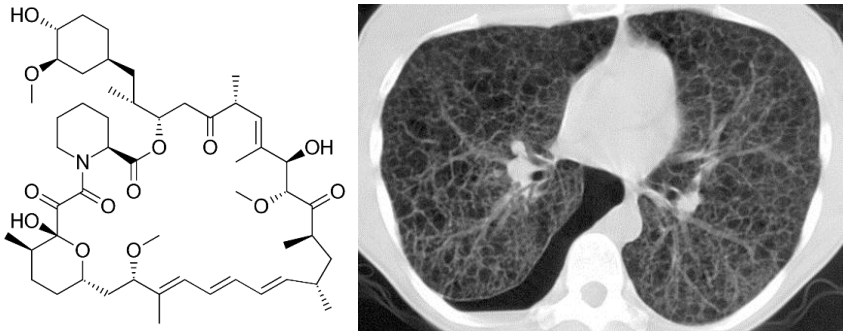

Figure-2: Sirolimus structure & lymphangioleiomyomatosis.

Sirolimus was first approved by the FDA in 1999 for the prophylaxis of organ rejection in patients aged 13 years and older receiving renal transplants. In November 2000, the drug was recognized by the European Agency as an alternative to calcineurin antagonists for maintenance therapy with corticosteroids. In May 2015, the FDA approved sirolimus for the treatment of patients with lymphangioleiomyomatosis. In November 2021, albumin-bound sirolimus for intravenous injection was approved by the FDA for the treatment of adults with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor (PEComa). Sirolimus was also investigated in other cancers such as skin cancer, Kaposi's Sarcoma, cutaneous T-cell lymphomas, and tuberous sclerosis. The topical formulation of sirolimus, marketed as HYFTOR, was approved by the FDA in April 2022: this marks the first topical treatment approved in the US for facial angiofibroma associated with tuberous sclerosis complex.[4]

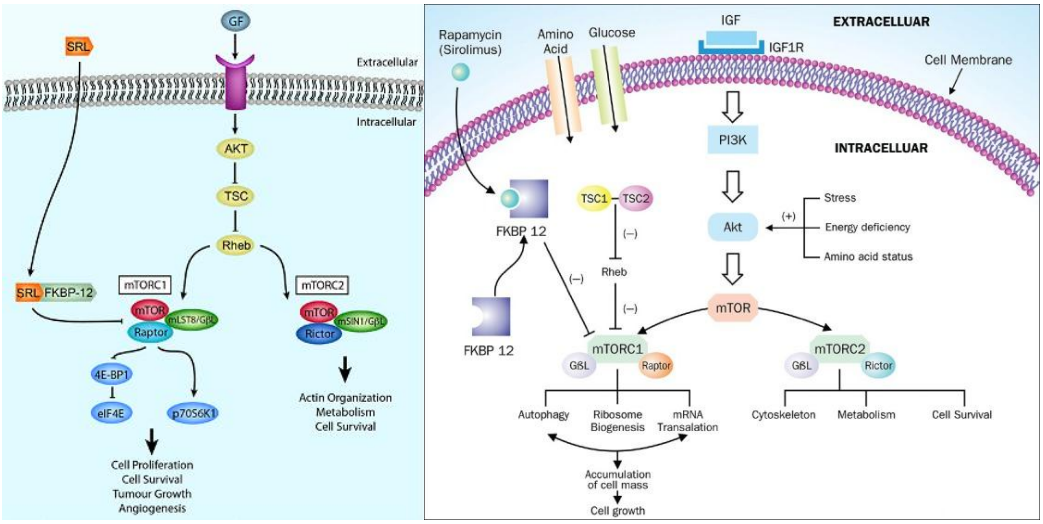

Figure-3: Mode of action of sirolimus.

Indication: Sirolimus is indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants. In patients at low-to moderate-immunologic risk, it is recommended that sirolimus be used initially in a regimen with cyclosporine and corticosteroids; cyclosporine should be withdrawn two to four months after transplantation. In patients at high-immunologic risk (defined as Black recipients and/or repeat renal transplant recipients who lost a previous allograft for immunologic reason and/or patients with high panel-reactive antibodies [PRA; peak PRA level > 80%]), it is recommended that sirolimus be used in combination with cyclosporine and corticosteroids for the first year following transplantation. It is also used to treat lymphangioleiomyomatosis. In the US, albumin-bound sirolimus for intravenous injection is indicated for the treatment of adult patients with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor (PEComa). In Europe, it is recommended that sirolimus for the prophylaxis of organ rejection in renal transplants is used in combination with cyclosporin microemulsion and corticosteroids for two to three months. Sirolimus may be continued as maintenance therapy with corticosteroids only if cyclosporin microemulsion can be progressively discontinued. Topical sirolimus is indicated for the treatment of facial angiofibroma associated with tuberous sclerosis in adults and pediatric patients six years of age and older.[5]

Pharmacodynamics: Sirolimus is an immunosuppressant drug with antifungal and antitumor effects. In animal models, sirolimus prolonged allograft survival following various organ transplants and reversed an acute rejection of heart and kidney allografts in rats. Upon oral administration of 2 mg/day and 5 mg/day, sirolimus significantly reduced the incidence of organ rejection in low- to moderate-immunologic risk renal transplant patients at six months following transplantation compared with either azathioprine or placebo. In some studies, the immunosuppressive effect of sirolimus lasted up to six months after discontinuation of therapy: this toleration effect is alloantigen-specific. Sirolimus potently inhibits antigen-induced proliferation of T cells, B cells, and antibody production. In rodent models of autoimmune disease, sirolimus suppressed immune-mediated events associated with systemic *lupus erythematosus*, collagen-induced arthritis, autoimmune type I diabetes, autoimmune myocarditis, experimental allergic encephalomyelitis, graft-versus-host disease, and autoimmune uveoretinitis.[6]

Figure-4: Sirolimus formulations.

Mechanism of action: Sirolimus works by inhibiting T-lymphocyte activation and proliferation stimulated by antigens and cytokines such as interleukin (IL)-2, IL-4, and IL-15. In target cells, sirolimus binds to the cytoplasmic receptor FK506-binding protein-12 (FKBP12), an immunophilin, to form an immunosuppressive complex. FKBP12-sirolimus complex binds to and inhibits the activation of the mammalian target of rapamycin (mTOR), which is a serine/threonine-specific protein kinase that regulates cell growth, proliferation, survival, mobility, and angiogenesis. mTOR regulates the downstream signaling pathways involved in cell survival, such as the phosphatidylinositol-3 kinase (PI3K)/Akt signaling pathway. Inhibition of mTOR leads to the suppression of cytokine-driven T-cell proliferation, thus the progression from the G1 to the S phase of the cell cycle is inhibited. Sirolimus also inhibits antibody production. *In-vitro*, sirolimus and other mTOR inhibitors inhibit the production of certain growth factors that may affect angiogenesis, fibroblast proliferation, and vascular permeability. Lymphangioleiomyomatosis is a disorder that primarily affects the lungs. It is characterized by lung tissue infiltration, unregulated alveolar smooth muscle proliferation, and cystic destruction of parenchyma. Although infrequent, it occurs as a symptomatic pulmonary complication in tuberous sclerosis complex (TSC), which is an inherited disorder caused by mutations in TSC genes. Loss of functional TSC gene leads to the aberrant activation of the mTOR signaling pathway, resulting in cellular proliferation and release of lymphangiogenic growth factors. Sirolimus inhibits the activated mTOR pathway and proliferation of alveolar smooth muscle cell proliferation.[7]

Absorption: In adult renal transplant patients with low-to moderate-immunologic risk, oral administration of 2 mg sirolimus led to a C_{max} of 14.4 ± 5.3 ng/mL for oral solution and 15.0 ± 4.9 ng/mL for oral tablets. The t_{max} was 2.1 ± 0.8 hours for oral solution and 3.5 ± 2.4 hours for oral tablets. In healthy subjects, the t_{max} is one hour. In a multi-dose study, steady-state was reached six days following repeated twice-daily administration without an initial loading dose, with the average trough

concentration of sirolimus increased approximately 2- to 3-fold. It is suspected that a loading dose of three times the maintenance dose will provide near steady-state concentrations within one day in most patients.[8]

The systemic availability of sirolimus is approximately 14%. In healthy subjects, the mean bioavailability of sirolimus after administration of the tablet is approximately 27% higher relative to the solution. Sirolimus tablets are not bioequivalent to the solution; however, clinical equivalence has been demonstrated at the 2 mg dose level. Sirolimus concentrations, following the administration of Rapamune Oral Solution to stable renal transplant patients, are dose-proportional between 3 and 12 mg/m^2.

Volume of distribution: The mean (± SD) blood-to-plasma ratio of sirolimus was 36 ± 18 L in stable renal allograft patients, indicating that sirolimus is extensively partitioned into formed blood elements. The mean volume of distribution ($V_{ss/F}$) of sirolimus is 12 ± 8 L/kg.

Protein binding: Sirolimus is 92% bound to human plasma proteins, mainly serum albumin (97%), α1-acid glycoprotein, and lipoproteins.

Metabolism: Sirolimus undergoes extensive metabolism in the intestinal wall and liver. Sirolimus is primarily metabolized by O-demethylation and/or hydroxylation via CYP3A4 to form seven major metabolites, including hydroxy, demethyl, and hydroxy demethyl metabolites, which are pharmacologically inactive. Sirolimus also undergoes counter-transport from enterocytes of the small intestine into the gut lumen.[9]

Route of elimination: Following oral administration of [^{14}C] sirolimus in healthy subjects, about 91% of the radioactivity was recovered from feces and only 2.2% of the radioactivity was detected in urine. Some of the metabolites of sirolimus are also detectable in feces and urine.[10]

Half-life: The mean ± SD terminal elimination half-life (t½) of sirolimus after multiple dosing in stable renal transplant patients was estimated to be about 62 ± 16 hours.[11]

Clearance: In adult renal transplant patients with low- to moderate-immunologic risk, oral administration of 2 mg sirolimus led to oral clearance of 173 ± 50 mL/h/kg for oral solution and 139 ± 63 mL/h/kg for oral tablets.[12]

Toxicity: Oral LD_{50} of sirolimus is 800 mg/kg in rats and 2500 mg/kg in mouse. Sirolimus is a narrow therapeutic index drug. Although there are reports of overdose with sirolimus, there is limited information on overdose in the clinical setting. Symptoms of overdose are consistent with the adverse effects of sirolimus. General supportive measures are recommended in the event of an overdose. Because sirolimus has low aqueous solubility and high erythrocyte and plasma protein binding, it is not expected to be dialyzable to any significant extent.[13]

Food Interactions: Avoid grapefruit products. Grapefruit inhibits the CYP3A4 metabolism of sirolimus and increases its serum concentration. Exercise caution with St. John's Wort. This herb induces CYP3A4 and P-gp; thus it may reduce sirolimus serum concentrations. Take with or without food. Take consistently with regard to food.[14]

Computed Properties

Table 1: Sirolimus properties.

Property Name	Property Value	Property Name	Property Value
Molecular Weight	914.2	Complexity	1760
XLogP3-AA	6	Isotope Atom Count	0
Hydrogen Bond Donor Count	3	Defined Atom Stereo center Count	15
Hydrogen Bond Acceptor Count	13	Undefined Atom Stereo center Count	0
Rotatable Bond Count	6	Defined Bond Stereo center Count	4
Exact Mass	913.55514157	Undefined Bond Stereocenter Count	0
Maonoisotopic Mass	913.55514157	Covalently-Bonded Unit Count	1
Topological Polar Surface Area	195 Å	Compound Is Canonicalized	Yes
Heavy Atom Count	65	Formal Charge	0

Chemical Taxonomy

Description: This compound belongs to the class of organic compounds known as macrolide lactams. These are cyclic polyketides containing both a cyclic amide and a cyclic ester group.[15]
Kingdom: Organic compounds
Super Class: Phenylpropanoids and polyketides
Class: Macrolide lactams
Direct Parent: Macrolide lactams
Alternative Parents: Alpha amino acid esters / Macrolides and analogues / Cyclohexanols / Piperidines / Oxanes / Tertiary carboxylic acid amides / Carboxylic acid esters / Cyclic alcohols and derivatives / Cyclic ketones / Hemiacetals
Substituents: Alcohol / Aliphatic heteropolycyclic compound / Alpha-amino acid ester / Alpha-amino acid or derivatives / Azacycle / Carbonyl

group / Carboxamide group / Carboxylic acid derivative / Carboxylic acid ester / Cyclic alcohol
Molecular Framework: Aliphatic heteropolycyclic compounds
External Descriptors: cyclic ketone, antibiotic antifungal drug, organic heterotricyclic compound, secondary alcohol, ether, lactam, macrolide, cyclic acetal, Plyenes.[16]

UV Spectra: UV max (95 percent ethanol): 267, 277, 288 nm (the absorbance of a solution containing one gram per 100 ml contained in a cell having an absorption path of one cm: 417, 541, and 416)

Therapeutic Uses: Sirolimus is indicated for the prevention of rejection of transplanted kidney allografts. It is recommended that sirolimus be used in a regimen with cyclosporine and corticosteroids. /Included in US product labeling/ Long-term results after percutaneous coronary intervention in the treatment of chronic total coronary occlusions is hindered by a significant rate of restenosis and reclusion. In the treatment of relatively simple nonocclusive lesions, sirolimus-eluting stents have shown dramatically reduced restenosis rates compared with bare metal stents, but whether these results are more widely applicable is unknown. The use of sirolimus-eluting stents in the treatment of chronic total coronary occlusions is associated with a reduction in the rate of major adverse cardiac events and restenosis compared with bare metal stents. Chronic renal failure triggered by calcineurin inhibitor (CNI)-based immunosuppression is a common complication after cardiac transplantation. Sirolimus and mycophenolate mofetil (MMF) are 2 newer immunosuppressive agents with no documented nephrotoxic side effects. This case report describes a patient with ongoing chronic renal failure 10 months after cardiac transplantation on cyclosporine-based immunosuppressive therapy. Conversion of the immunosuppressive regimen from cyclosporine to sirolimus and MMF resulted in freedom from acute rejection, excellent cardiac graft function and consistently improved renal function. This case illustrates the beneficial potential of sirolimus and MMF as CNI-free and safe long-term immunosuppression in a patient with chronic renal failure after heart transplantation.[17]

Drug Warnings: Increased susceptibility to infection and the possible development of lymphoma and other malignancies may result from immunosuppression increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression.[18] Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should use Rapamune. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient. The safety and efficacy of Rapamune (sirolimus) as immunosuppressive therapy have not been established in liver or lung transplant patients, and therefore, such use is not recommended.[19] Liver Transplantation - Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis (HAT): The use of Rapamune in combination with tacrolimus was associated with excess mortality and graft loss in a study in de novo liver transplant patients. Many of these patients had evidence of infection at or near the time of death. In this and another study in de novo liver transplant patients, the use of Rapamune in combination with cyclosporine or tacrolimus was associated with an increase in HAT; most cases of HAT occurred within 30 days post-transplantation and most led to graft loss or death. Lung Transplantation - Bronchial Anastomotic Dehiscence: Cases of bronchial anastomotic dehiscence, most fatal, have been reported in de novo lung transplant patients when Rapamune has been used as part of an immunosuppressive regimen.[20]

CONCLUSION

Sirolimus is used together with other medicines to prevent the body from rejecting a transplanted kidney. It belongs to a group of medicines known as immunosuppressive agents. When a patient receives an organ transplant, the body's white blood cells will try to get rid of (reject) the transplanted organ. During transplant rejection, the transplanted organ stimulates lymphocytes in the body to multiply in response to certain molecules. Sirolimus inhibits the lymphocytes from multiplying in response to these molecules. Sirolimus is in a class of medications called immunosuppressants. It works by suppressing the body's immune system.

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