Topical rapamycin (sirolimus) for facial angiofibromas

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ABSTRACT

Rapamycin (sirolimus) is a fungal fermentation product that inhibits the proper functioning of a serine/threonine protein kinase in mammalian cells eponymously named mammalian target of rapamycin, or mTOR. Rapamycin is a novel class of anticancer and immunosuppressant drugs targeting the proteins at molecular level. Rapamycin (sirolimus) is routinely incorporated in drug-eluting stents used for cardiac angioplasty. In recent years, rapamycin was found to be efficacious in managing the symptom complex of tuberous sclerosis, i.e. renal angiomyolipoma, giant cell astrocytoma and pulmonary lymphangiomyomatosis. Various investigators have also proved that topically applied rapamycin causes regression of facial angiofibromas, giving better cosmetic results.

Key words: Facial angiofibromas, Mechanism of action, Rapamycin, Tuberous sclerosis

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Rapamycin is a lipophilic macrocyclic lactone which was first isolated from a soil bacterium *Streptomyces hygroscopicus* in Rapa Nui (Easter Island) in 1965,hence the name rapamycin.[1] Though rapamycin was shown to have antifungal properties, later on it was discovered to possess anti-T cell activity and was being used as immunosuppressant in prevention of graft rejection.[2] Rapamycin belongs to a novel class of anti-cancer drugs called as mTOR (*m*ammalian *t*arget *o*f *r*apamycin) inhibitors.

mTOR (*m*echanistic *t*arget *o*f *r*apamycin) is a large atypical conserved serine-threonine kinase enzyme complex involved in cellular growth, stress, aging and vasculogenesis with a molecular weight of 290 kDa.[3,4] mTOR pathway is critical for normal cell function as it plays a pivotal role in integrating signals from nutrients, energy status and growth factors to regulate many homeostatic processes, including autophagy, ribosome biogenesis and metabolism modulated by phosphatidylinositol 3- kinases (PI3K)–Akt-dependent mechanisms. Although mammalian cells possess only single mTOR gene located on short arm of chromosome 1p36.2, mTOR pathway is composed of two distinct functional complex proteins- (i) mTORC1 consisting of mTOR, LST8/GβL (*G* protein *b*eta subunit-*l*ike) and *r*egulatory-*a*ssociated *p*rotein of m*TOR* (raptor) and (ii) mTORC 2 consists of mTOR, GβL, and *r*apamycin *i*nsensitive *c*omponent of mTOR (rictor).[5] It is to be noted that only mTORC 1 is inhibited by rapamycin and not mTORC2.

Functionally, mTORC1 is mainly responsible for the nutrient-sensitive functions of TOR, whereas TORC2 plays a chief role in cytoskeletal reorganization and cell survival. Under normal circumstances, mTOR signaling causes cell proliferation and is under tight regulation of proteins like tuberin and hamartin. Hamartin and tuberin are the protein products of the tuberous sclerosis genes (TSC1 and TSC2) located on chromosome 9 and 16 respectively.[6] Physiologically, the hamartin-tuberin complex activates the protein *R*as *h*omolog *e*nriched in brain (*Rheb*) and exerts inhibitory control over mTOR.[7] Mutation in these two genes (TSC1 and TSC2) leads to defective functioning of these protein products and results in constitutive activation of mTOR pathway, leading to leading to phosphorylation of downstream targets including p70S6K (p70 S6 kinase) and 4E-BP1 (*e*ukaryotic initiation factor *4E-b*inding *p*rotein 1) culminating in protein synthesis and abnormal cellular proliferation as evident in hamartomas of tuberous sclerosis.[8] Rapamycin can simulate the action of tuberin and hamartin protein and thus can prevent the procarcinogenic action of mTOR signaling.

Mechanism of Action of Rapamycin [Figure 1]

Rapamycin belongs to the class of macrocyclic immunosuppressive drugs that are active only when bound to immunophilins. Cyclosporine and tacrolimus (FK506) are other members who also act via binding to immunophilins.[9] Intracellularly, rapamycin binds to FKBP12 (*FK binding protein* 12 kDa), an immunophilin and forms a complex FKBP12-rapamycin. mTOR possess a binding domain portion called FKBP12-rapamycin binding domain (FRB). After binding to FRB domain of mTOR protein, FKBP12-rapamycin complex potently inhibits the activity of mTORC1 complex via autophosphorylation and dissociation of mTORC1 complex and thus blocking the binding of mTOR to its substrates.[10] Inhibition of mTOR pathway blocks cytokine-driven T-cell proliferation by inhibiting the progression from the G1 to the S phase of the cell cycle,thus explaining its role in immunosuppression.

Indications

Currently, the only FDA approved indication for rapamycin is to prevent organ rejection after transplant surgery.[11,12] Off-label indications include topical treatment of facial angiofibromas[13,14] systemic treatment for renal angiomyolipoma[15] lymphangioleiomyomatosis.[16,17] brain tumors associated with tuberous sclerosis[18,19] and for chemotherapy of various malignancies (renal and hepatocellular cancer and mantle cell lymphomas).[20,21] Other conditions where rapamycin has been used are Kaposi sarcoma,[22] psoriasis[23] and lichen planus.[24]

Pharmacodynamics/Pharmacokinetics

Rapamycin is very poorly water soluble, severely limiting its bioavailability. Congeners of rapamycin have been developed with better pharmacokinetic properties i.e temsirolimus (CCI-779), everolimus (RAD001) and ridaforolimus (AP23573) and are collectively known as *rapalogs*. Currently rapamycin (sirolimus) is available in the market in two formulations: Rapamune® oral solution (60mg per 60ml in an amber colored bottle) and Rapamune® tablet available in 1mg (white triangular-shaped tablet) and 2 mg (yellow-to-beige triangular-shaped tablet) strength.[25] Oral solution needs to be kept at cold temperature of 2-8° centigrade.

Topical Rapamycin for Angiofibromas Associated with Tuberous Sclerosis

Angiofibromas shows prominent vascular component owing to increased expression of angiogenic factors like vascular endothelial growth factor (VEGF) and mTOR overactivation that promotes angiogenesis as discussed earlier. Inhibition of mTOR pathway decreases the output of VEGF by inhibiting hypoxia-inducible factor (HIF) expression and by directly repressing VEGF-stimulated endothelial cell proliferation.[26]

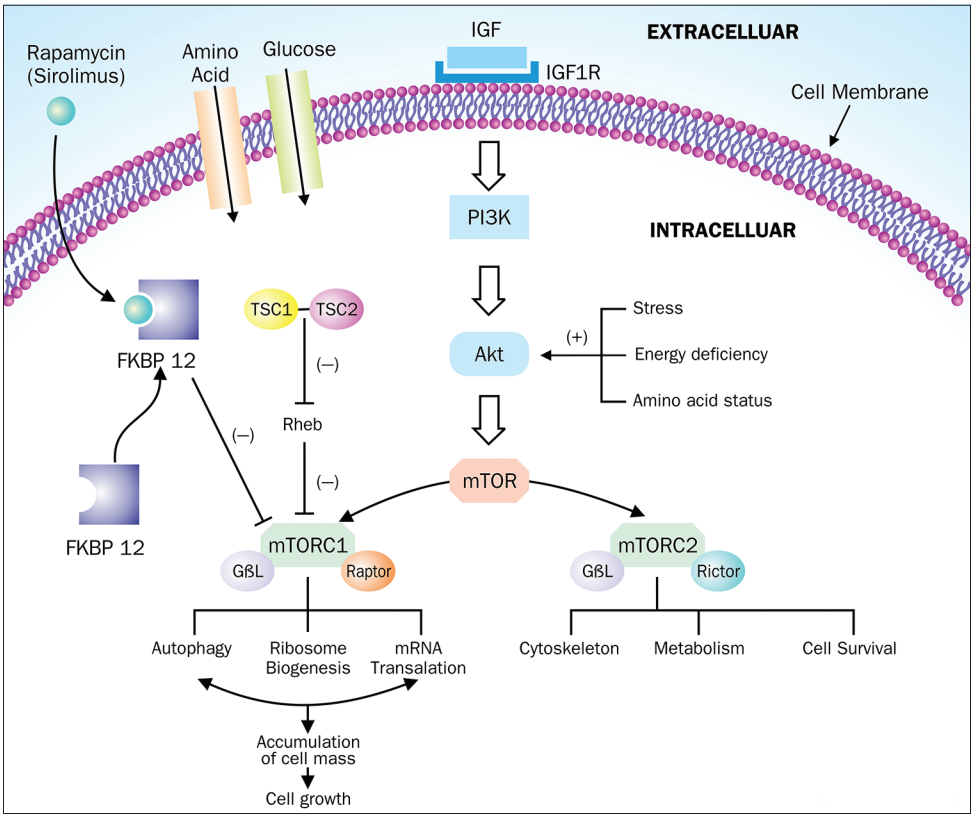

Figure 1: Mechanism of action of rapamycin: Intracellularly rapamycin binds to FKBP12 protein and binds to *mTORC1* thereby inhibiting its downstream pathway. Protein products of *TSC 1* and *TSC 2* gene i.e. hamartin and tuberin inhibits the functioning of *mTORC1* pathway via *Rheb* protein and thus mutation of these TSC proteins causes constitutive activation of mTOR pathway leading to cellular proliferation

Table 1: Topical rapamycin used for treatment of facial angiofibromas

Authors	Number of patients	Formulation used	Frequency and duration
Haemel et al.[27]	One	1% rapamycin ointment prepared from rapamycin tablet	Twice a day for 12 weeks
Wataya-Kaneda M and colleagues [13]	Nine	0.2% rapamycin ointment in 0.03% tacrolimus[a] as a vehicle	Twice daily for three months
Mutizwa MM, et al.[28]	Two	Oral rapamycin solution (1mg/ml) available commercially was used topically	Twice daily for 10-23 weeks
Truchuelo T, et al.[29]	One	Topical rapamycin 1% with Dexeryl® cream as a vehicle	Once a day for one month
Foster RS, et al.[30]	Four	0.1% rapamycin prepared from crushed 1 mg sirolimus tablets in petrolatum	Twice a day for 6 months
Salido R, et al.[31]	Ten	Sirolimus 0.4% ointment compounded in petrolatum	Three times a week for 9 months
Kaufman McNamara E and colleagues[32]	Two	Compounded product composed of 60 mL of rapamycin 1 mg/ml) solution and 60 g of emollient	

a: Tacrolimus does not possess inhibitory action on mTOR pathway mTOR: mammalian target of rapamycin; TSC: Tuberous sclerosis gene; PI3K: phosphatidylinositol 3- kinases; FKBP: FK binding protein

Facial angiofibromas are a chief cause of concern among the patients having TSC owing to unsightly appearance of facial papules. Rapamycin is a large molecule, difficult to formulate in the ointment form.[13] Various investigators have used different concentrations of topical rapamycin for the management of facial angiofibromas [Table 1].

Irritation and burning sensation is the most common side effect seen after topical rapamycin. Patients should be prescribed topical hydrocortisone 0.1% cream or desonide 0.05% lotion along with liberal emollients to counteract any irritation and ensure compliance. It is practical to use commercially available oral solution of rapamycin (1 mg/ml) as a topical formulation since compounding pharmacies are not always readily accessible and the stability and efficacy of compounded preparation cannot be ensured. The major limiting factor in prescribing topical rapamycin is the high cost of the medication. Haemel *et al.* compounded topical rapamycin from crushed rapamycin tablet into a 30 ml of 1% ointment and it priced about $3000.[28] Topical rapamycin can be safely prescribed in children in whom angiofibromas are still in the growing phase.[27,30] Patients receiving rapamycin therapy should avoid taking grapefruit juice as it inhibits the metabolism of rapamycin akin to cyclosporine.

Systemic Side Effects

Topically applied rapamycin has minimal systemic absorption, precluding any adverse systemic effects. If facilities are available, trough drug levels should be monitored by chromatographic and immunoassay methodologies. However, whether this applies to topical rapamycin therapy needs to evaluated. More robust studies are required to evaluate the extent of systemic absorption of topically applied rapamycin and to determine the safety of topically administered rapamycin.

CONCLUSION

Topical rapamycin appears to be a promising and effective way of treating facial angiofibromas which are cosmetically disfiguring in patients with TSC. Topical rapamycin needs to be studied in a larger cohort of subjects to determine the duration and frequency of application. The major disadvantage is the cost of therapy which is prohibitively expensive at the present date in our resource poor setting.

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