Topical Sirolimus in the Treatment of Facial Angiofibromas

Tuberous sclerosis (TS) is an autosomal dominant neurocutaneous syndrome. It is characterized by the presence of hamartomatous growths in different organs, including brain, skin, kidneys, and heart. Among the hamartomatous lesions, facial angiofibromas occur in 80% of individuals with TS. Although usually asymptomatic, facial angiofibromas are cosmetically disfiguring and have a negative psychological impact on pediatric patients. The current treatments for facial angiofibromas include physically destructive techniques such as excision, cryosurgery, curettage, dermabrasion, chemical peeling, and laser therapies including CO₂ laser and pulsed dye laser. The procedures are associated with the inherent risks of anesthesia, scarring and can be painful with a prolonged post-operative recovery. On account of variable recurrence rates with these procedures, repeated treatments are often necessary. Hence, from a long-term perspective, none of these treatments are satisfactory.

Sirolimus is a lipophilic macrocyclic lactone which was first isolated from a soil bacterium, Streptomyces hygroscopicus in Rapa Nui (Easter Island) in 1965, hence the old name rapamycin.

Hofbauer et al. reported a case of TS complex with facial angiofibromas that improved after using systemic sirolimus following a renal transplant. Since systemic sirolimus is expensive, may cause carcinogenesis, hypersensitivity reactions, hypercholesterolemia, and hypertension; topical application was considered an alternative. Haemel et al. were the first to use sirolimus topically, and since then, sirolimus has been the most studied mammalian target of rapamycin (mTOR) inhibitor in the past 10 years. The molecular weight of the sirolimus being 914.2 g/mol allows absorption of the molecule through the superficial layers to the deep layers of the epidermis.

There are certain pertinent aspects in the treatment of facial angiofibromas with topical sirolimus that needs elaboration and is the purpose of this editorial. Each aspect has been dealt with in a question-and-answer format for the ease of understanding.

**What is the Mechanism of Action of Sirolimus in Facial Angiofibromas?**

In TS, there is aberrant activation of mTOR in fibroblast-like cells in the dermis. This leads to the production of epiregulin which is a growth factor that stimulates epidermal cell proliferation. The overproduction of epidermal cells in conjunction with enhanced angiogenesis is responsible for the clinical appearance and the continued progression of angiofibromas.

Sirolimus binds with high specificity to mTOR and leads to inhibition of mTOR activity and ultimately downregulation of cell growth. So also, it has an inhibitory effect on the vascular endothelial growth factor (VEGF) that leads to repression of VEGF-induced endothelial proliferation.

**When to Start Topical Sirolimus in the Treatment of Angiofibromas?**

On account of the potent inhibition of VEGF by sirolimus, the vascular component of the angiofibromas responds better and earlier than the fibrous component. It is proven through histopathological analysis that the fibrous component of angiofibromas increases with age. Hence, to achieve best results, it is advisable to start topical sirolimus at an earlier age; as soon as, the lesions appear. In children, since the skin is thinner and more permeable, the percutaneous absorption is greater allowing a better clinical response.

Hence, it is best given as monotherapy at an early age, for small low volume angiofibromas with a predominant vascular component. However, we still do not know whether prolonged therapy in childhood will the minimize formation of new lesions or will it cause lesions to form less rapidly in adulthood.

In adults with predominant fibrous component or with severely disfiguring larger angiofibromas, physical modalities are preferred. Topical sirolimus can be added on later to decrease the chances of recurrence. But what we do not know as yet, is how long one should wait before applying sirolimus on a prior surgically treated area considering the possibility of delayed healing because of topical Sirolimus. But then, there is also a possibility that we may get a better response on account of enhanced penetration of topical Sirolimus on the treated area.

**What are the Formulations of Topical Sirolimus Used in Literature?**

High variability exists regarding the composition of the topical compounds (tablets or powder of rapamycin, in solution, cream, or ointment form), concentration of active ingredient (from 0.003% to 1%), frequency of application (once or twice daily or intermittent), number of months to observe improvement (1–3 months), and recurrence after discontinuation of treatment (1–3 months).

In India, sirolimus is available as 1-mg and 2-mg tablets. The tablets can be powdered and combined with desired ointment/cream/gel base to get a topical preparation.

Most studies have utilized petrolatum or white soft paraffin as the base. The advantage of using white soft paraffin as a base is that since sirolimus is lipophilic, homogeneous distribution of the medication is possible with a depot effect. In addition, it has an additional moisturizing and an occlusive effect and is
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Systemic absorption of the topical formulation has not found to be significant. In the study by Wataya-Kaneda et al., utilizing 0.2% sirolimus hydrophilic gel, low blood levels of rapamycin were detected in several patients, particularly in the pediatric subgroup (50% and 100% in the adult subgroup and pediatric subgroup, respectively), resulting in the likely occurrence of systemic side effects.[10]

**HOW LONG CAN ONE CONTINUE TOPICAL SIROLIMUS?**

A recurrence can be expected within 2 months of discontinuation of topical sirolimus. Recurrences happen because of a cytostatic rather than a cytotoxic effect of sirolimus on the neoplastic cells. Daily application is necessary since a gradual worsening was observed over a period of months when the frequency of application was reduced to thrice weekly. Hence, a patient would require long-term, uninterrupted treatment to maintain benefit. The longest duration reported is 30 months with 19 patients without any recurrence of lesions or loss of effectiveness.[11]

In the Indian setting, considering that the cost of the compounded ointment may go up to Rs. 200 per day when a concentration of 1% sirolimus is used, applying the preparation continuously may not be feasible, and hence, reduction in the frequency of application to 2–3 times per week after adequate clinical response is achieved can be tried.[6,7] This regimen is also likely to enhance compliance. In cases of recurrence, sirolimus has been demonstrated to have good efficacy on repeated use.[12]

**CONCLUSION**

As per the available literature, though not a cure, topical sirolimus appears to be a safe and effective modality of treatment in the facial angiofibromas of TS. Long-term safety, efficacy, and durability of response need to be assessed. Its use as a prophylaxis in the facial angiofibromas remains to be explored. Efficacy, tolerability, and safety in the Indian setting need to be assessed, the major limiting factor being the cost of the medication.

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cheap. The downside is that the cutaneous bioavailability may be limited since it may not be completely solubilized in the formulation and this may affect efficacy. It may give rise to an uncomfortable oily, gritty sensation on the face and can lead to acne and folliculitis. The solid fragments of the powdered tablet can at times cause bleeding. It is advisable to run the compound through the ointment mill three or more times to avoid this complication.

In the literature available from India, the concentration of sirolimus in white soft paraffin used is 0.1% used twice daily in the initial phase followed by 1% twice daily with no major cutaneous or systemic adverse events.[6,7] It is proposed that a concentration of 0.1% for pediatric patients, 0.5% for older children, and 1% for teenagers and adults with larger protuberant lesions can be optimal.

Sirolimus has also been used in combination with topical tacrolimus and commercially available creams such as Skincerity, Eucerin, and Dexeryl as vehicles. However, compounding powdered tablets in a base is a labor-intensive process, and quality variation is possible in each batch.

Oral sirolimus solution has been tried as a topical preparation but unfortunately is not yet available in India. Irritation and burning sensation are reported with this formulation, possibly on account of high surfactant levels.

To negotiate the side effects of an ointment base, Bouguéon et al. proposed a cream containing 0.1% sirolimus solubilized in Transcutol and mixed with a marketed cream (Excipial) with stability achieved over 85 days.[8]

As an advancement, Le Guyader et al. have proposed a surfactant-free hydroalcoholic gel containing sirolimus solubilized in ethanol with addition of glycerol, urea, Carbopol, and α-tocopherol as excipients in an attempt to improve cutaneous penetration and tolerability. This preparation has been found to have long-term stability for over a year at +4° and -20°.[9]

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**HOW EARLY ARE THE EFFECTS OF TOPICAL SIROLIMUS SEEN?**

Early effects in the form of a decrease in the erythema associated with the angiofibromas are seen as early as 4 weeks after starting topical sirolimus.

**WHAT ARE THE SIDE EFFECTS OF TOPICAL SIROLIMUS?**

The topical application is usually well tolerated, and the side effects are usually mild Department of Pediatric Dermatology, irritation and perioral dermatitis. Mild irritant contact dermatitis was reported with the solution that was easily manageable with topical corticosteroids.
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