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Case Report

Topical sirolimus for the treatment of facial angiofibromas in tuberous sclerosis patient: a case report

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ABSTRACT

Tuberous sclerosis complex (TSC) is an autosomal-dominant neurocutaneous disorder seen in 1/6000 births. Facial angiofibroma is the most common cosmetic disfiguring cutaneous manifestation of it. Therapeutic modalities include cryotherapy, podophyllotoxin application, electrocoagulation, surgery and laser therapy associated with their own high risk of complications and sequelae. Sirolimus is a lipophilic lactone isolated from *Streptomyces hygroscopicus* (soil bacteria), found to have anti-T-cell properties and classifies as an anticancer drug from the mammalian target of rapamycin (mTOR) inhibitors. Sirolimus binds with mTOR and causes inhibition of mTOR activity and VEGF-stimulated endothelial cell proliferation. Topical preparation produced by crushing tablets of sirolimus 1 mcg and mixing in an aqueous base emollient or the solution form of sirolimus has been used with beneficial effects in the treatment of angiofibroma, especially in younger patients. Here we reported a case of a 34-year-old male, a known case of TSC with facial angiofibroma in which the topical 0.1% sirolimus had been used with beneficial effects and clinical outcomes.

Keywords: Tuberous sclerosis complex, Angiofibroma, mTOR inhibitors, Sirolimus

INTRODUCTION

TSC is an autosomal-dominant neurocutaneous disorder caused by the mutations in two genes: tuberous sclerosis complex 1 on 9q34.3 coding protein hamartin and tuberous sclerosis complex 2 on 16p13.3 coding protein tuberin. These suppressor proteins inhibit the mTOR.[1] Any mutation of these genes results in inhibition of this regulatory process leading to uncontrolled cell proliferation, growth and synthesis of protein and resulting in multisystem hamartomas.[2] The incidence of this disorder is seen in 1/6000 births and mostly affects the skin, in patients with TSC older than 5 years.[3-5] Therapeutic modalities include cryotherapy, podophyllotoxin application, electrocoagulation, surgery and laser therapy associated with their own high risk of complications and sequelae.[4] On the other hand, clinical outcomes of these treatments are unsatisfactory due to the frequent recurrence of the lesions and are difficult to administer in patients with extensive angiofibromas or severe intellectual impairment.

Sirolimus is a lipophilic lactone isolated from *S. hygroscopicus* (soil bacteria), found to have anti-T-cell properties and classifies as an anticancer drug from the mTOR inhibitors.[6] It is used as an immunosuppressant to prevent graft rejection in renal transplants and is incorporated routinely in drug-eluting stents in cardiac

angioplasty. Systemic use of sirolimus is expensive, carcinogenic and causes hypersensitivity reactions, hypercholesteremia, and hypertension. Hence, topical preparation produces by crushing tablets of sirolimus 1 µg and mixing in an aqueous base emollient or using the solution form of sirolimus.

In the present case report, we discussed the effect of the sirolimus gel 0.1%, in patients with TSC and the problems faced with the use of its use in the Indian scenario.

CASE REPORT

A 34-year-old male, a known case of TSC presented to the outpatient department for the cosmetic disfiguring facial angiofibromas for the last 2.5 years. He was diagnosed according to the Roach and Sparagana criteria and using podophyllin toxin. The patient complained of recurrence of the lesion within a short period after cessation of podophyllin toxin. To avoid podophyllin related complications, topical 0.1% sirolimus was planned to start.

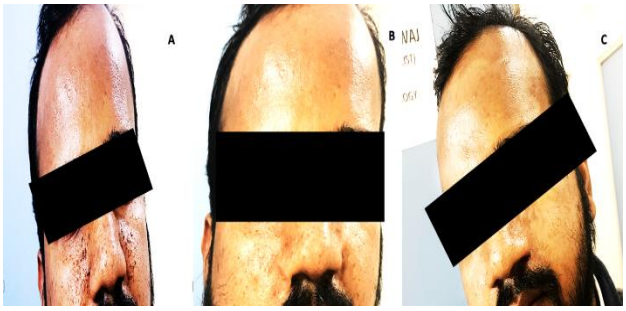

Figure 1: (A) Pre-treatment image; (B) after 3 months of topical 0.1% sirolimus ointment twice daily; (C) after 1 month of topical 1% sirolimus ointment twice daily.

Topical 0.1% sirolimus was prepared by the pharmacy. The tablets of 1 mg of sirolimus were crushed and mixed with Moisturex™ composed of urea IP 10%, lactic acid IP 10%, propylene glycol IP, light liquid paraffin IP 10% with preservatives methylparaben IP 0.16% and propylparaben IP 0.04%. The prepared mixture was stored in a rigid plastic container. Before initiation of treatment complete blood count and hepatic and renal functions tests of the patients were done and found to be okay.

The patient was asked to apply the preparation over the lesions twice daily. The patient was advised to stop the application of preparation and report immediately if any redness or tenderness develops. The photograph of the lesion was taken before the beginning of treatment and after one month gap of consecutive three months. The patient was evaluated using the facial angiofibroma severity index by Salido-Vallejo et al.[6] We had seen a definite decrease in the erythema as well as the size of the facial angiofibromas (Figure 1). Encouraged by the positive results; in an attempt to accelerate the clinical response, we increased the concentration of sirolimus to 1% which was used for a period of 2 months with a decrease in the size as well as a number of angiofibromas with the substantial decrease in the erythema (Figure 1).

The patient did not experience any cutaneous adverse effects throughout the treatment. It was not possible to measure the systemic absorption of the sirolimus on the account of cost constraints.

DISCUSSION

TSC includes angiofibroma, fibrous forehead plaques, hypomelanotic macules or confetti-like lesions, periungual fibromas and shagreen patches.[7] Facial angiofibromas are small, symmetrical and numerous pink to reddish papules or nodules which coalesce to form plaques typically located on the cheeks, nose and chin. These papules are composed of blood vessels and fibrous tissue and are seen approximately in 80% of patients making them the most frequent cutaneous finding. Many patients also developed hypomelanotic macules and ungual fibromas.[8,9] Based on International Tuberous Sclerosis Complex Consensus Conference 2012, these are considered as the major diagnostic criteria.[10] Although benign in nature, they can obstruct nasal openings and can bleed. Skin lesions are permanent and cause significant psychological concerns to appearance and impair a patient's quality of life.

Current treatment modalities like vascular and ablative lasers and other lesion destructive techniques such as cryosurgery, dermabrasion, shave excision, photodynamic therapy and electrodesiccation. These proactive and costly approaches have no sustained efficacy on long-term bases. The risks of complications like scarring continue to exist.

Various studies reported the use of mTOR inhibitor sirolimus and everolimus as a targeted therapy for the renal and neurological manifestations of TSC.[11,12] The role of sirolimus in TSC was first seen in a patient of TSC who was receiving oral sirolimus after undergoing renal transplantation. The patient showed pronounced regression in her cutaneous angiofibromas. Later this triggered used as a topical agent, in an attempt to minimize systemic toxicity. mTOR is aberrantly active in fibroblast-like cells located within the dermal layer of the skin in patients with TSC.[13]

Fibroblast cells produce an epidermal growth factor, epiregulin, which stimulates epidermal cell proliferation resulting in the generation of epidermal cells at a rate faster than their sloughing ability from the skin surface. The overproduction of epidermal cells in conjugation with angiogenesis results in the primary appearance and continued further progression of facial angiofibromas. TSC angiofibroma has a prominent vascular component

which increases the expression of angiogenic factors like vascular endothelial growth factor (VEGF) and mTOR. This overactivation promotes angiogenesis. Sirolimus binds with mTOR and causes inhibition of mTOR activity and downregulation of cell growth. mTOR also inhibits the progression of the cell cycle from the G1 phase to the S phase, suppresses T lymphocyte and antibody production, and keratinocyte proliferation inhibition and neutrophilic inflammatory activity.[9,10] With mTOR pathway inhibition there is inhibition of hypoxia-inducible factor expression leads to decreases output of VEGF. Inhibition of mTOR also directly represses VEGF-stimulated endothelial cell proliferation.[14,15]

A molecular weight of 914.2 g/mol, allows sirolimus to absorb through the superficial layers of the epidermis to the deep dermal layer.[16] Growing tumours with greater proliferative components during the early stages of life could be more sensitive to the sirolimus mTOR inhibitory actions. Initiation of treatment as soon as angiofibromas start appearing can give more clinically justifiable results. In various reports, investigators had used different topical sirolimus concentrations for varying duration for the management of facial angiofibromas. The preparation formulated in an aqueous base is well tolerated with no adverse effects and is also cost-effective in comparison to various other treatment modules.

The limitation of this study was the resource-constrained due to which monitoring of serum sirolimus level was not done.

CONCLUSION

Topical sirolimus can be considered as an option of treatment for facial angiofibromas as it has fewer side effects in comparison to the other treatment modalities and is easy to apply. A significant rise in the cost of the medication with increasing concentration, of sirolimus from 0.1 to 1% could be a limiting factor. Though the literature mentioned minimal systemic absorption on topical application of sirolimus, it should have been monitored using chromatographic and immunoassay methodologies, which was not possible in a resource-constrained setting.

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REFERENCES

1. Chopra M, Lawson JA, Wilson M, Kennedy SE, Taylor P, Buckley MF, et al. An Australian tuberous sclerosis COHORT: are surveillance guidelines being met? J Paediatr Child Health. 2011;47(10):711-6.
2. Wheless JW, Almoazen H. A novel topical rapamycin cream for the treatment of facial angiofibromas in tuberous sclerosis complex. J Child Neurol. 2013;28(7):933-6.
3. National Organization for Rare Disorders (NORD). Fact sheet: Tuberous sclerosis. Available at: https://rarediseases.org/rare-diseases/tuberous-sclerosis. Accessed on 14 May 2022.
4. Schwartz RA, Fernández G, Kotulska K, Jóźwiak S. Tuberous sclerosis complex: advances in diagnosis, genetics, and management. J Am Acad Dermatol. 2007;57(2):189-202.
5. Webb DW, Clarke A, Fryer A, Osborne JP. The cutaneous features of tuberous sclerosis: a population study. Br J Dermatol. 1996;135(1):1-5.
6. Salido R, Garnacho-Saucedo G, Cuevas-Asencio I, Ruano J, Galán-Gutierrez M, Vélez A, et al. Sustained clinical effectiveness and favorable safety profile of topical sirolimus for tuberous sclerosis – Associated facial angiofibroma. J EurAcad Dermatol Venereol. 2012;26(10):1315-8.
7. Paghdal KV, Schwartz RA. Sirolimus (rapamycin): From thesoil of Easter Island to a bright future. J Am Acad Dermatol. 2007;57(6):1046-50.
8. Ng KH, Ng SM, Parker A. Annual review of children with tuberous sclerosis. Arch Dis Child Educ Pract Ed. 2015;100(3):114-21.
9. Tonekaboni SH, Tonekaboni SH, Tousi P, Ebrahimi A, Ahmadabadi F, Keyhanidoust Z, et al. Clinical and para clinical manifestations of tuberous sclerosis: a cross sectional study on 81 pediatric patients. Iran J Child Neurol. 2012;6(3):25-31.
10. Krueger DA, Northrup H; International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex surveillance and management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013;49(4):255-65.
11. Birca A, Mercier C, Major P. Rapamycin as an alternative to surgical treatment of subependymal giant cell astrocytomas in a patient with tuberous sclerosis complex. J Neurosurg Pediatr. 2010;6(4):381-4.
12. Krueger DA, Care MM, Holland K, Agricola K, Tudor C, Mangeshkar P, et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. N Engl J Med. 2010;363(19):1801-11.
13. Li S, Takeuchi F, Wang JA, Fan Q, Komurasaki T, Billings EM, et al. Mesenchymal-epithelial interactions involving epiregulin in tuberous sclerosis complex hamaratomas. Proc Natl Acad Sci U S A. 2008;105(9):3539-44.
14. Hofbauer GF, Marcollo-Pini A, Corsenca A, Kistler AD, French LE, Wüthrich RP, et al. The mTOR inhibitor rapamycin significantly improves facial angiofibroma lesions in a patient with tuberous sclerosis. Br J Dermatol. 2008;159(2):473-5.
15. Haemel, AK, O'Brian AL, Teng JM. Topical rapamycin: a novel approach to facial angiofibromas in tuberous sclerosis. Arch Dermatol. 2010;146(7):715-8.

16. Koenig M, Hebert A, Roberson J, Samuels J, Slopis J, Woerner A, et al. Topical rapamycin therapy to alleviate the cutaneous manifestation of tuberous sclerosis complex-a double blind, randomised, controlled trial to evaluate safety and efficacy of topically applied rapamycin. Drugs R D. 2012:12(3):123-6.

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