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Original Article

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Topical Rapamycin - Tacrolimus Combination for Facial Angiofibromas in Tuberous Sclerosis – A Pilot Study of 5 Cases

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Abstract

Background: Facial angiofibroma represents the most conspicuous and cosmetic disfiguring cutaneous manifestation of tuberous sclerosis, frequently leading to stigma for both the affected individuals and their families. Many times these angiofibromas are left untreated due to the dearth of minimally invasive therapeutic modalities. To combat this issue, topical administration of the mammalian target of rapamycin (mTOR) inhibitor, rapamycin, is recommended.

Objective: The study aimed to evaluate the safety, tolerability, and efficacy of a topical combination of rapamycin and tacrolimus for the treatment of facial angiofibromas associated with tuberous sclerosis complex (TSC).

Materials and Methods: This was a pilot study of 5 patients. A topical formulation was prepared by mixing 0.1% rapamycin with 0.1% tacrolimus 10 g ointment. Patients were instructed to apply the medication topically twice daily over the angiofibroma for 12 weeks, with regular follow-up visits every 3 weeks. We investigated the efficacy and safety using the "Facial angiofibroma severity index" (FASI).

Results: The mean "facial angiofibroma severity index (FASI)" score was 8 ± 1.0, 6.4 ± 1.14, and 5.2 ± 0.84 at 0, 6, and 12 weeks, respectively, which was statistically significant. Transient irritation occurred in one patient.

Conclusion: The topical combination of rapamycin and tacrolimus shows potential as an effective and well-tolerated option for facial angiofibroma. Limitations of the study include a small sample size and a relatively short follow-up duration.

Key words: Angiofibromas, Rapamycin, Tacrolimus, Tuberous Sclerosis

Introduction

Tuberous sclerosis complex (TSC), an autosomal dominant neurocutaneous disorder, is a prototypical mTORpathy, resulting from inactivating pathogenic mutations in TSC1 and TSC2.[1] TSC1 occurs on the distal q-arm of chromosome 9 (9q34) and encodes protein hamartin. TSC2 occurs on the distal p-arm of chromosome 16 (16p13.3) and encodes protein tuberin.[1] Loss of TSC1 or TSC2 genes, leads to constitutive activation of the mammalian target of rapamycin (mTOR) signalling pathway leading to uncontrolled cell proliferation and formation of hamartomas in various organs.[2]

Cutaneous manifestations include hypomelanotic macules, facial angiofibromas, forehead plagues,

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shagreen patches, periungual and gingival fibromas;[3] Various treatments for facial angiofibromas include laser, surgery, cryotherapy or dermabrasion. However, these modalities can cause pain, lead to scarring and is ineffective in preventing recurrence.[4,5]

These observations suggest that mTOR inhibitors represent a new drug in the treatment armamentarium for TSC. Oral administration of rapamycin has proven effective for treating astrocytomas, renal angiomyolipomas, lymphangioleiomyomatosis, and facial angiofibromas associated with TSC.[6] However, cost is a limiting factor with the use of oral rapamycin. It may also cause carcinogenesis, hypersensitivity reactions, hypercholesterolemia and hypertension.[7] Therefore, topical rapamycin is recommended as an alternative for cutaneous lesions.

Rapamycin is a large molecule, so it's difficult to formulate an easily absorbable ointment. Tacrolimus has a structure similar to rapamycin. Both tacrolimus and rapamycin are competitive inhibitors of FKBP12. Tacrolimus –FKBP12 complex inhibits calcineurin while the sirolimus –FKBP12 complex directly inhibits mammalian target of rapamycin (mTOR) complex1 (mTORC1), thereby inhibiting the mTOR pathway.[4] In this study, topical combination of rapamycin and tacrolimus (0.1%) ointment was used and photographs were taken pre-treatment, after 6 weeks and 12 weeks of treatment.

Material and Methods

The study began after approval by the Ethics Committee for Clinical Research(NHLIRB/2019/AUG/6th/No.01). It was a pilot, open, non-randomized, prospective interventional study. Patients diagnosed with Tuberous Sclerosis Complex according to "Roach and Sparagana criteria" presenting to the outpatient department of dermatology were included in the study.[8] Patients with infection at local site, history of chronic renal failure and those showing inability to come for follow up were excluded from the study. Each patient with facial angiofibroma was sequentially included in the study after written informed assent.

Patients were explained in detail about the duration of treatment, possible side effects and prognosis of treatment. Patients experiencing irritation and burning sensation after topical rapamycin were withdrawn from the study.

Topical rapamycin 0.1% was prepared by crushing 10 tablets of rapamycin 1 mg and mixing in 0.1% tacrolimus 10 g ointment as a vehicle in our department using mechanical weighing scale.

Patients were once demonstrated about how to apply and then asked to apply the cream twice daily with regular follow up every 3 weeks for 12 weeks. Clinical photographs were taken pre - treatment and during each subsequent follow-up. The effectiveness of topical combination of rapamycin and tacrolimus was assessed using "facial angiofibroma severity index" created by *Salido-Vallejo et al*. [Table – 1] which is obtained by adding erythema, size and extent of lesions of facial angiofibroma.[9] Mean scores were calculated pre-treatment, after 6 weeks and 12 weeks of treatment.

Table 1: The "facial angiofibroma severity index", designed by *Salido -Vallejo et a.l*[9]

Facial angiofibroma severity index (FASI):

1) Erythema
   a) Skin color = 0
   b) Light red = 1
   c) Red = 2
   d) Dark red/purple = 3

2) Size
   a) Small (≤5mm) = 1
   b) Large (≥5 mm) = 2
   c) Confluent = 3

3) Extension
   a) <50% cheek surface = 2
   b) >50% cheek surface = 3

4) FASI score (Sum of the above parameters)
   a) Mild: ≤ 5
   b) Moderate: 6-7
   c) Severe: ≥ 8

Results

In the study, 5 patients, under 25 years, who provided informed assent were enrolled. (Table-2). The mean "facial angiofibroma severity index (FASI)" score was 8 ± 1.0, 6.4 ± 1.14 and 5.2 ± 0.84 at 0, 6 and 12 weeks respectively. The mean score was statistically significantly lower at 6 and 12 weeks of treatment i.e. p = 0.0028 and p = 0.0002 respectively compared to score at the beginning [Figure – 6]. Standard deviation pre-treatment and post-treatment were 1.00 and 0.84 respectively. 95 percent confidence interval was between 2.24 to 3.35 and Cohen's d was 0.447. Transient irritation was experienced by one patient after application. The irritation subsided as the lesions subsided.

Table 2: Summary of patient profile and results of study

	Case 1	Case 2	Case 3	Case 4	Case 5
Age/Sex	7Y/F	6Y/F	20Y/M	24Y/F	18Y/F
Other. clinical features of TS	Shagreen patch, ash leaf macules	Shagreen patch, fibrotic plague, epilepsy	Shagreen patch, ash leaf macules	Shagreen patch, epilepsy	Shagreen patch
Concentration of rapamycin used (%)	0.1	0.1	0.1	0.1	0.1
Duration of rapamycin use at the time of follow up (weeks)	12	12	12	12	12
FASI score pre treatment	7	7	9	8	9
FASI score post treatment	4	5	6	5	6
Percentage (%) Reduction in FASI Score	33.33%	22.22%	33.34%	33.33%	33.34%

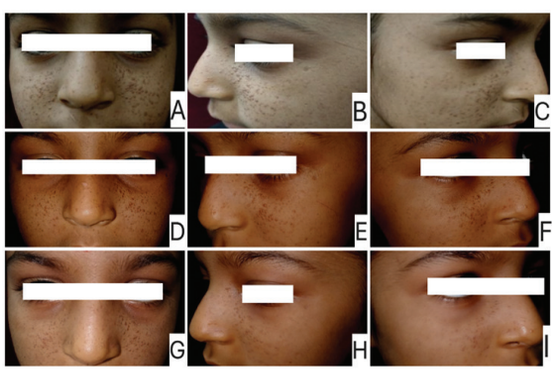

Figure 1: A, B, C – Pretreatment (FASI - 7), D, E, F - After 6 weeks of treatment (FASI – 6), G, H, I - After 12 weeks of treatment (FASI – 4)

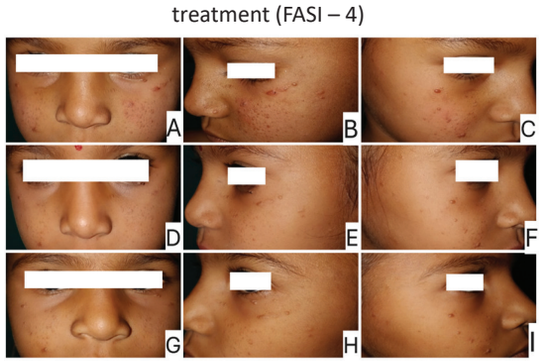

Figure 2: A, B, C – Pretreatment (FASI - 7), D, E, F - After 6 weeks of treatment (FASI – 5), G, H, I - After 12 weeks of treatment (FASI – 5)

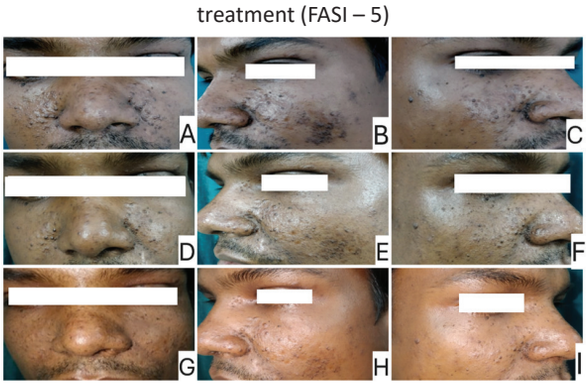

Figure 3: A, B, C – Pretreatment (FASI - 9), D, E, F - After 6 weeks of treatment (FASI – 8), G, H, I - After 12 weeks of treatment (FASI – 6)

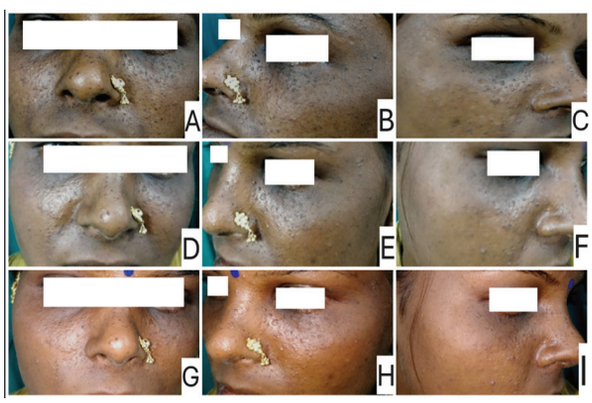

Figure 4: A, B, C – Pretreatment (FASI - 8), D, E, F - After 6 weeks of treatment (FASI – 6), G, H, I - After 12 weeks of treatment (FASI – 5)

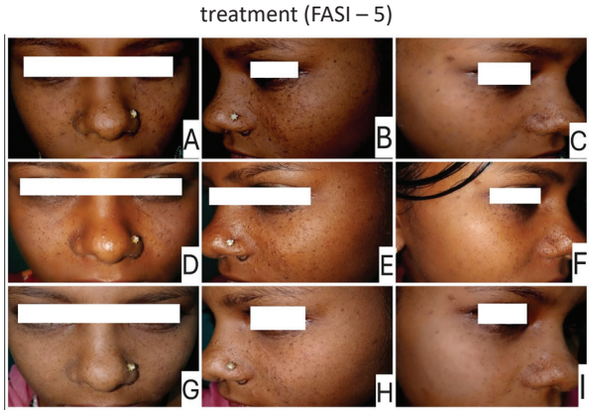

Figure 5: A, B, C – Pretreatment (FASI - 9), D, E, F - After 6 weeks of treatment (FASI – 7), G, H,I - After 12 weeks of treatment (FASI – 6)

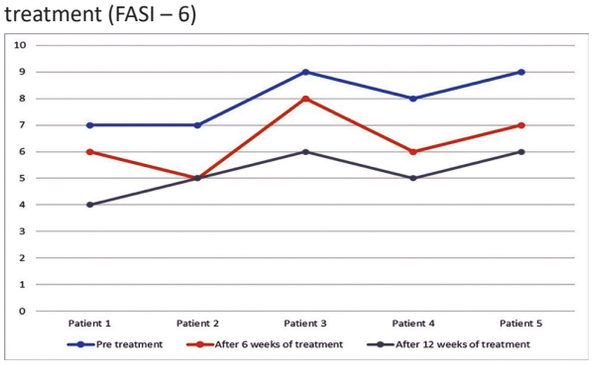

Figure 6: The "Facial Angiofibroma Severity Index" (FASI) of 5 patients measured over a period of time

Discussion

Tuberous Sclerosis (TS) is an inherited multisystem autosomal dominant disorder characterized by hamartomas in brain, skin, eyes, heart, lungs and kidneys.[10] Various type of skin lesions can occur in TS of which angiofibroma is the most common feature which develops in most affected individuals by 5 years of age. Facial angiofibromas can cause distress because of their appearance and are prone to bleeding.[11] Physical removal of facial angiofibromas through dermabrasion, excision, curettage, cryosurgery, electrocoagulation or laser therapy are effective approaches but are associated with risk of complication and recurrence of lesions.[12]

Facial angiofibroma also called fibrous papules or adenoma sebaceum are dome shaped, skin-coloured to red papules symmetrically on the cheeks, nasolabial folds, nose and chin with telangiectasia on the surface of papule. Angiofibromas have a prominent vascular component due to increased expression of angiogenic factors like vascular endothelial growth factor (VEGF) and mTOR overactivation leading to increased angiogenesis.[5] mTOR is a protein kinase, inhibition of which results in reduced protein synthesis, induction of apoptosis and decreased expression of vascular endothelial growth factor (VEGF) thereby reducing angiogenesis and tumor progression. Calcineurin inhibitors impair IL-2 transcription, reducing T cell activation, while mTOR inhibitors block cell cycle progression downstream of IL-2 signaling, suppressing both T and B cell proliferation. Mechanistically, CNIs and mTOR inhibitors act at distinct but complementary points in immune cell signalling, together providing robust immunosuppression by targeting different steps in cytokine-mediated proliferation.[21]

mTOR inhibitors (Sirolimus/Rapamycin) initiated for renal transplant in a TSC patient reduced facial angiofibroma dramatically. Since then, the effect of sirolimus in facial angiofibroma is investigated. Systemic sirolimus apart from being expensive, may cause adverse effects. Hence topical sirolimus was considered for use which has now become the cornerstone for management of tumors associated with tuberous sclerosis. Only a few reports of application of topical combination of rapamycin and tacrolimus have been documented in English literature.[5,13,14,15,16]

A study done by *Cinar et al* used tab rapamycin to prepare study product as applying topical solution of sirolimus directly to the skin lead to irritation.[12] The tablets were pulverized and mixed with white soft paraffin. In our study, we crushed the tablet form of rapamycin 1mg and mixed it with tacrolimus (0.1%) to a concentration of 0.1%. Another practical advantages of using tacrolimus in combination with rapamycin is the ease of formulation as 0.1% tacrolimus is used in an ointment base. Its base, typically composed of emulsifying agents and a lipid-rich carrier, makes it relatively easy to combine with other topical agents, such as rapamycin, which is less commonly available in a suitable topical form. However, no effect was observed when 0.03% tacrolimus ointment was used alone for treating facial angiofibroma in the past.[4] The mild improvement noted with tacrolimus alone might be attributed to stripping instead of the pharmacological effects of tacrolimus itself.[4]

Our results were similar to study by *Kaneda et al*.[4] In this study, at the end of the treatment, all of the patients significantly improved on rapamycin–tacrolimus treatment compared to tacrolimus alone. No adverse reactions were noted. In our study, all 5 patients showed a statistically significant improvement in TSC with the rapamycin–tacrolimus combination. It is quite possible that the effect may be due to synergistic activity of rapamycin and tacrolimus, as isolated efficacy of rapamycin was not evaluated.

Side effects are infrequently encountered as systemic levels of rapamycin are low or undetectable when applied topically at a concentration of 0.1% to 1%.[17,18,19,20] Patients were monitored clinically for side effects, as our patients applied low concentrations of rapamycin over a small body surface area. Based on these results, the topical combination therapy of rapamycin and tacrolimus seems to be a safe and effective treatment for TSC-related angiofibromas. Finally, our patients were monitored for 3 months, and longer follow up is required to observe durability of response as the possibility of recurrence is very high.

Limitations of the study include small sample size, no control arm, no systemic monitoring. statistical analysis limited by sample size and shorter duration of follow up.

Conclusion

Commercial Availability of topical preparations of rapamycin is not uniform or scarce hence it is useful to prepare a topical formulation form the easily available rapamycin tablets. Topical combination therapy is deemed to be safe and effective treatment in all patients for facial angiofibromas with fewer side effects and ease of application.

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