Topical Rapamycin

A Novel Approach to Facial Angiofibromas in Tuberous Sclerosis

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REPORT OF A CASE

A 16-year-old girl presented with a complex medical history that was related to both systemic and cutaneous manifestations of TS. In addition to her cutaneous manifestations of progressive facial angiofibromas that she has had since she was 5 years old and, more recently, gingival fibromas, she also had renal angiopomas, severe mental retardation, and epilepsy with complex partial seizures that generalize. She had been placed on a regimen of several antiepileptic medications, currently oxcarbazepine and divalproex sodium, for control of intractable seizures. At 10 months of age, she underwent open heart surgery for removal of a rhabdomyoma that was blocking her pulmonary artery. At 13 years of age, she underwent endoscopic removal of a cranial intraventricular mass, with pathologic examination demonstrating subependymal giant cell astrocytoma, followed by placement of a ventriculostomy for relief of obstructive hydrocephalus. Also, she underwent multiple shave excisions and repeated treatments with both pulsed dye and carbon dioxide lasers, with at least 1 treatment per year over the last 3 years, to control bleeding and rapid progression of facial angiofibromas. Despite these aggressive interventions, her facial lesions remained prominent, progressive, and disfiguring, with a tendency toward recurrence and new lesions. The procedural treatments had no lasting effects on the progression of her condition.

SOLUTION

Rapamycin is an immunosuppressant that is traditionally used in transplant recipients. However, this molecule also has promising antineoplastic effects that are exerted through the downregulation of angiogenesis and the correction of aberrant growth signals, which are implicated in many tumors and cancers.4,5 Recently, several studies have suggested that rapamycin therapy may be an effective treatment for the neoplasms associated with TS. For instance, oral rapamycin therapy was shown to reduce the volume of TS-associated visceral angiomyolipomas.6 Also, a patient with TS who was receiving oral rapamycin after undergoing renal transplantation had pronounced regression of her cutaneous angiofibromas.2 While systemic exposure and adverse effects would be undesirable in the treatment of cutaneous disease, a small clinical trial of topical rapamycin for psoriasis suggested that topical delivery may be feasible and safe.7 Therefore, we hypothesized that the topical application of rapamycin could be a novel and practical therapeutic option for facial angiofibromas in patients with TS. Because a topical preparation of rapamycin is not commercially available, a 1% ointment was custom com-
pounded for compassionate use in our patient. Rapamycin was extracted from tablets to be used for the ointment, and petrolatum was used as the major ingredient in the vehicle to minimize irritation. The compounded medication is intended for use within 3 months. Because the ointment is not produced for commercial use at this time, extended stability testing was not performed. We estimate that 0.5 g of ointment was used with each application, for a total of 5 mg of topical rapamycin.

Before beginning the topical treatment, the patient was noted to have numerous facial angiofibromas measuring approximately 0.5 to 4 mm in greatest dimension and diffusely involving the glabella and temples, with more prominent involvement of the central area of the face and the nasal bridge (Figure, A and B). Topical rapamycin therapy (1% ointment) was initiated twice daily. At 1 week, the patient’s parents reported decreased erythema. Shortly thereafter, they noted gradual improvement in her skin texture. Although she could not communicate verbally, she did not appear to experience any discomfort when the medication was applied.

At the 6-week follow-up visit, the patient was noted to have a reduced number of angiofibromas and improved facial erythema. The vascular papules on both cheeks were much smaller. The lesions on the temples and forehead were completely resolved. This striking improvement had never been achieved with previous procedural treatments. At the 12-week reassessment, the patient showed a sustained effect, with continued improvement in skin texture (Figure, C and D). Laboratory tests were performed at 6 weeks and 12 weeks to evaluate potential systemic adverse effects. Complete blood cell counts and the results of a complete metabolic panel remained stable at baseline. The serum rapamycin level remained under 2 ng/mL (below the limits of detection; reference range, 4-20 ng/mL). Therefore, no measurable systemic absorption was detected after 3 months’ application of 1% topical rapamycin to approximately 1% of the body surface area (BSA). Therefore, topical rapamycin therapy could be an effective treatment for facial angiofibromas, with minimal systemic toxic effects.

**COMMENT**

Rapamycin belongs to a novel group of molecules known as the mTOR (mammalian target of rapamycin) inhibitors and is approved for use in renal transplantation and drug-eluting stents in the United States. The molecular mechanisms of rapamycin are complex, and its signaling pathways have only recently been partially understood. In addition to its recognized immunosuppressive effects, this molecule demonstrates antineoplastic activity both in vitro and in vivo. Rapamycin exerts this effect by decreasing production of the proangiogenic molecule VEGF (vascular endothelial growth factor), which is implicated in many cancers, as well as by inhibiting its downstream signaling. Other topical immunosuppressive agents such as calcineurin inhibitors do not demonstrate these effects.

Furthermore, rapamycin appears to correct aberrant signaling in a variety of pathways that regulate cell growth and apoptosis, including those activated in some tumor states, such as TS. Tuberous sclerosis is an autosomal dominant tumor syndrome that results from mutations in the tumor suppressors hamartin (TSC1) or tuberin (TSC2). Hamartin and tuberin normally suppress mTOR, which increases cell cycle progression when it is released from negative regulation. The loss of tumor suppressive function in TS leads to the formation of multiple tumors of the internal organs and skin. Although treatment options for TS, including facial angiofibromas, have previously been limited, reconstitution of mTOR inhibition by rapamycin may represent a targeted therapy to prevent and treat tumors.
There are several recent studies that support the feasibility of topical delivery. A topical preparation of rapamycin, 8%, in a capric acid–benzyl alcohol vehicle was recently shown to penetrate normal skin and appeared to have anti-inflammatory activity in a study of 24 patients with psoriasis. One drawback to the preparation used in the clinical psoriasis study was that the vehicle may have contributed to local irritation in 3 patients. To avoid such local adverse effects, we used a petrolatum-based vehicle for our patient, and the treatment was very well tolerated, without signs of local irritation. Note that tacrolimus, which is chemically similar to rapamycin, also exerts its biologic function effectively in a similar vehicle. Additional study in a TS mouse model has demonstrated that topical rapamycin ointments, 0.4% and 0.8%, could inhibit tumor growth effectively when applied to a very large BSA, resulting in systemic absorption.

Our patient did not demonstrate detectable serum rapamycin levels after 3 months of application to her face. Furthermore, there were no changes in blood cell counts or chemistry profiles from baseline or other evidence of systemic adverse effects of rapamycin therapy. We believe that systemic toxic effects with the 1% preparation applied to a limited BSA are unlikely. Similarly, in a previous report an 8% topical preparation applied to 1% to 5% of the BSA did not result in measurable systemic levels or laboratory abnormalities in patients with psoriasis. The systemic absorption observed in murine studies could be related to the vehicle used or to the surface area treated. Because of the high BSA to body mass index, the rapamycin dosage per body mass unit was quite high in this animal model.

While the effects seen in the present case are exciting, large-scale clinical trials are needed to validate the safety and effectiveness of this novel treatment for facial angiofibromas. Specific considerations requiring further investigation include any local or systemic consequences of long-term therapy because patients may need prolonged treatment. Compliance was not an issue in our patient because of the excellent response she had to the treatment. At the time of this report, she is still using the medication daily. Therefore, we cannot presently offer practical insight into whether the lesions will recur after downtitration or discontinuation of the therapy. However, this issue certainly merits further systematic investigation because regrowth has been noted with renal angiomyolipomas after discontinuation of oral rapamycin therapy. Finally, further evaluation of the potential for systemic absorption should be performed, particularly with respect to smaller children and infants. Although we believe that accidental transfer of small amounts to the mouth or eyes should be considered in young children, we do not think that this will pose any serious health risk. The utility of rapamycin eye drops for treating conditions such as macular degeneration has been limited by poor absorption across the outer surface of the eye, with potential applications presently focused on ocular surface conditions such as keratoconjunctivitis sicca as a result.

In summary, current data suggest that topical rapamycin ointment can be an effective treatment for recalcitrant facial angiofibromas in patients with TS. The treatment appears to be well tolerated with no evident local or systemic adverse effects. Furthermore, it avoids the risks of general anesthesia and surgical complications and appears to produce more sustained effects than procedural treatments. Finally, given the effects of rapamycin therapy on both angiogenesis and cell division, topical preparations may ultimately find broader application for a variety of benign (eg, infantile hemangioma) and malignant (eg, Kaposi sarcoma) cutaneous vascular lesions.

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Author Contributions: Dr Teng had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Haemel and Teng. Acquisition of data: Teng. Analysis and interpretation of data: Haemel, O’Brien, and Teng. Drafting of the manuscript: Haemel, O’Brien, and Teng. Critical revision of the manuscript for important intellectual content: Haemel, O’Brien, and Teng. Administrative, technical, or material support: Haemel and Teng. Study supervision: Teng.

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REFERENCES


The Best of the Best

Top-Accessed Article: Hair Removal in Pigmented Skin


This was a nonrandomized study that analyzed the clinical and histologic effects of the Nd:YAG laser as a hair removal device. The study showed that laser hair removal could be done safely with minimum dyspigmentation and other adverse effects in the 20 women who were skin types IV through VI. The article also provided the degree of response (70%-90%), the response at different body sites (face, axilla, and leg), the duration (over a 12-month period), and the findings of histologic analysis. The work behind this article opened up the field of laser hair removal to all skin types. It also helped create a new treatment option for diseases that are centered around the hair follicle, such as pseudofolliculitis barbae and hidradenitis suppurativa.

From June 2004 through August 2009, this article was viewed 3575 times on the Archives of Dermatology Web site.

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