Topical rapamycin in facial angiofibromas: patients satisfaction *versus* objective response, and a literature review

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Summary

Facial Angiofibromas (FA) are a common cutaneous manifestation of Tuberous Sclerosis (TS). Different therapies have been employed until now (surgery, CO_2 laser…) without successful and permanent effects. Recently, topical rapamycin has been reported as a new and effective treatment without significant adverse effects.
We present our experience in four adult patients with FA and TS who have been treated with 1% rapamycin ointment for three months. We evaluated the objective response achieved by using the Facial Angiofibromas Severity Index (FASI). On the other hand, in order to know the patients' subjective satisfaction they completed a questionnaire to evaluate this therapy.
We noticed a slight reduction of erythema, size and number of FA, lower than published in the literature. Despite this, overall satisfaction was high or very high even if the FA reappeared months after discontinuing the application.
We wonder if this subjective response justifies the costs of this treatment nowadays, especially in adult patients in which the established fibrosis in the FA could decrease the efficacy of the ointment. We also present a review of all published cases to date.

KEY WORDS: rapamycin; angiofibromas; tuberous sclerosis; survey.

Introduction

Facial Angiofibromas (FA) are a common cutaneous manifestation of Tuberous Sclerosis (TS). This genodermatosis also affects the kidney, brain and heart. It is caused by a mutation in TSC1 or TSC2 genes that code for the mTOR pathway inhibitors, hamartin and tuberin respectively (1). The lack of these proteins leads to persistent activation of this pathway and the development of multisystem hamartomatous tumors. Angiofibromas constitute an important aesthetic problem with psychological impact but no effective treatment.
Sirolimus (or rapamycin) is an inhibitor of the mTOR pathway, which suppresses the growth of visceral tumors. This molecule was obtained from a soil bacterium *Streptomyces hygroscopicus* (2). Its antifungal properties were first described, but later it showed anti-T cell activity, so it started to be used to prevent rejection after solid organ transplants. In 2008, Hofbauer et al. described an improvement in FA in one patient with TS during the administration of oral sirolimus after a renal transplant (1). Systemic administration of rapamycin can cause thrombocytopenia, leukopenia, anemia, urinary infection, hypercholesterolemia or hypertriglyceridemia. Therefore it is not justified unless the hamartomas involve vital organs. Haemel et al. suggested topical application of rapamycin to avoid its systemic side effects (3). Their approach was based on an animal model and a clinical trial on patients with psoriasis treated with 1% sirolimus ointment. Several cases of FA improvement with this treatment have been published since then (2-14).

Objective, material and methods

We present our experience in four patients of 25, 45, 48 and 43 years old (1 female, 3 males) with FA and TS. All of them had been previously treated with surgery and CO_2 laser achieving a partial improvement. Topical 1% rapamycin ointment was prescribed bid for three months. It was formulated with commercialized 2 mg rapamycin tablets and white petrolatum. We aim to evaluate the objective clinical changes, the side effects occurred and the patient's subjective improvement after three months of treatment, and also three months after discontinuing the application. The FASI (Facial Angiofibromas Severity Index) score of assessment of FA proposed by Salido et al. (4) was used to measure the presence or lack of improvement. This

Table 1 - Facial Angiofibromas Severity Index (FASI) Score (4).

FASI (Facial Angiofibromas Severity Index) SCORE	
Erythema	0-3
Size	0: none 1: small 2: large 3: confluent
Extension	2: < 50% of the cheek surface 3: > 50% of the cheek surface

score is based on the presence of erythema and the size and extension of FA (Table 1) and the result is the sum of the scores of each item (4). In addition to it, the patients completed a questionnaire evaluating the tolerability of the ointment, the benefits and disadvantages of its application, and their personal satisfaction with it.

Results (Table 2)

The average of pre-treatment FASI was: 7, 4, 9 and 5. Erythema reduction, decrease in number and size of FA was observed, achieving a reduction in FASI of 34, 11, 11 and 11,5%, with an average of 16,875%. After three months of rapamycin 1% application the FASI was 4 (Figure 1), 3, 8 and 4 respectively. Erythema reduction was the first visible effect. The administration frequency had to be reduced only in the first patient due to irritation. Long term response after treatment was only observed in one of the four patients. Preliminary results show a tendency to recurrent lesions since one month after finishing the application.
According to the patient's answers to the questionnaire, overall satisfaction during the three months of treatment with rapamycin was high or very high in 3 of the 4 patients. Furthermore, it showed that 3 of them remained satisfied even after reappearance of the lesions three months after treatment was finished. All of them would repeat this therapy if possible and would recommend it to other patients with FA.

Discussion

The effectiveness of topical rapamycin in FA has been widely reported (2-14). A review of existing evidence is

Table 2 - Objective and subjective results after three months of treatment.

	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4
Pre-treatment FASI	7	4	9	5
Post- treatment FASI	4	3	8	4
Reduction of number of FA	++	+	+	-
Reduction of size of FA	++	++	+	+
Reduction of erythema	++	-	++	+
Other effects		Reduction of bleedings of FA after minor trauma		
Side effects	Local irritation→ She reduced to one application/day	"Sensation of oily skin"	None	None
Subjective global response	Very good	Good	Good	Poor
AFTER THREE MONTHS OF DISCONTINUING APPLICATION				
Sustained response	No	Yes	No	No
Reappearance of FA	Yes, as previous	No, for the moment	Yes, even more than before treatment	Yes, as previous
Global satisfaction	Very high	High	Intermediate	Poor

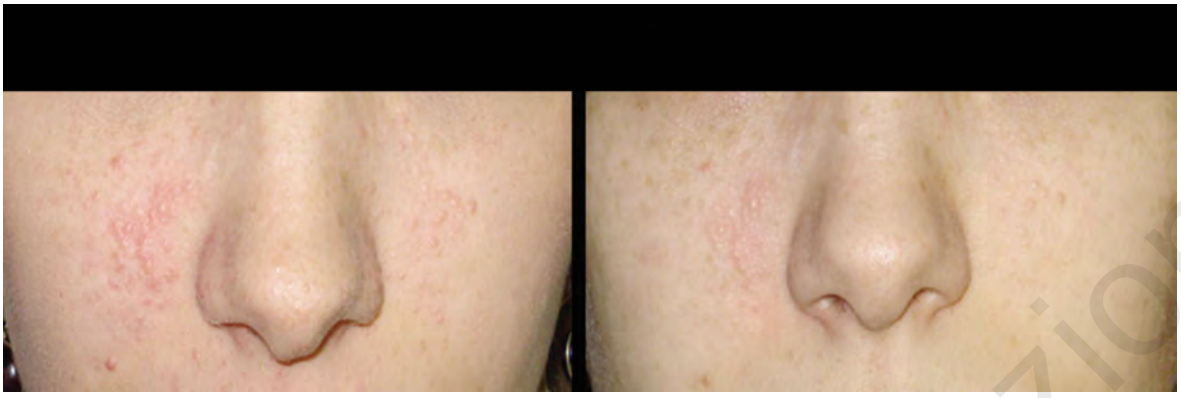

Figure 1 - Results in patient 1: FASI 7 pre-treatment (left). FASI 4 post-treatment (right).

summarized in Table 3. It has been tested in different formulations by using crashed rapamycin tablets: 1% in petrolatum for 12 weeks (3), in petrolatum with 0,4% of rapamycin three times a week for nine months (4), and also in a 0,2% concentration in 0,03% tacrolimus ointment (5). It has been reported its direct use as commercialized rapamycin solution (1mg/ml) (6, 7) and even as a blending of this solution in moisturizing cream (8). It has recently been proposed to use polyvinylidene fluoride as a vehicle to improve its organoleptic properties (9).

All these have shown reduction not only of erythema but also in the number of FA in patients with TS. The most common adverse effect was local irritation, as occurred in one patient of our series. This seems to be more severe with the rapamycin solution than with the ointment (6-7), although it was usually well-managed by reducing the dosage to once daily, with emollients or applying 1% hydrocortisone cream for 2-3 days (6). The application of topical rapamycin should be avoided in recent wounds, because it could modify the healing process (4, 15). Several studies have reported that sirolimus plasmatic concentration remains undetectable even in daily application (3, 5, 6, 10, 11). These determinations were not made in our patients.

Although subjective global satisfaction was high, the objective improvement of our series was not as significant as expected. This may be due to several factors. On one hand the average age of our series (40,25) was older than the reviewed in the literature [16 (3), 17,9 (4), 21,77 (5), 20,5 (6), 8,5 (7), 13,5 (8), 17,6 (11), 11 (12), 27 (13), 10,6 (14)]. In fact it is supposed that the younger patients have an earlier and greater response to topical rapamycin (4, 7, 11, 15). It is possible that FA in children and teenagers are less fibrotic than those of older patients in which fibrosis is established. Indeed the greatest improvement in our series was in the youngest patient (25 years old) (Figure 1), the same case that presented local irritation. This is why we wonder if irritation is in some way related to efficacy. On the other hand it is possible that a longer period of treatment could be necessary to achieve more significant results.

Different patterns are now under research and it is possible that better results could be obtained with less frequent application, more prolonged in time however (i.e. 2-3 applications per week for 9-12 months) (4, 5, 14). Also, lower concentrations of rapamycin [0,4% (4), 0,2% (5, 11), 0,03% (10)] are obtaining good results with longer application.

Recurrence of FA has also been noted after one month of discontinuing the treatment. The first sign is reappearance of erythema and then the growth of FA. This fact has already been reported (3, 5, 7, 11, 14).

Nevertheless, our four cases were highly or very highly satisfied with this topical product. We believe this is because we offer them a non-aggressive treatment for lesions without effective therapies so far. Moreover, patients realize that the single decrease of erythema constitutes an evident aesthetic improvement. As a matter of fact, all of them would recommend this treatment to other people with their condition and they would repeat the application of the ointment if possible. Only one patient complained about the sensation of oily skin left by the ointment, but it could be solved by changing the vehicle.

Concerning the pharmacoeconomic issue, in our center, the cost of 30 grams of 1% rapamycin ointment was 232,42€. It was prepared with crushed commercialized 2 mg rapamycin tablets, which makes the product expensive. We wonder if this partial and transient improvement justifies the costs nowadays. Some authors have reported lower costs and better blending by buying the active molecule in powder form (16). This way, a low cost cream could be justified in some cases with this good subjective response, especially in children.

In conclusion, although promising results have been reported with topical rapamycin in FA, the objective response in older patients is less significant, suggesting that topical rapamycin effectiveness decreases with age. However, subjective satisfaction was very high. More confortable dosages and lower sirolimus concentration are now under research pointing the reduction in cost and improvement of tolerance, especially considering chronic application in order to maintain a long course response.

Table 3 - Summary of the reviewed literature (3-14).

Authors	Number of cases	Age of patients	Formulation used	Dosage	Duration of treatment	Improvement	Time to onset of improvement	Side effects	Post-treatment follow-up	Recurrence of FA	Time to recurrence
Haemel et al. (3) July 2010	1	16	1% rapamycin in petrolatum	Twice daily	3 months	Yes	1 week	None	NS	NS	NS
DeKlotz et al. (9) Sept 2011	1	NS	1% rapamycin in petrolatum	Twice daily	1 month	Yes	NS	NS	NS	NS	NS
Wataya-Kaneda et al. (5) Oct 2011	9	9-46	0.2% rapamycin in 0.03% tacrolimus ointment	Twice daily	3 months	Excellent 2/9 Good 3/9 Mild 4/9	6 weeks	None	NS	Yes	1 month
Mutizwa et al. (6) Oct 2011	2	15-26	Commercially available oral rapamycin solution (1 mg ML^{-1})	Once daily due to local irritation	23 weeks	Yes	10 weeks	2/2 local irritation	NS	NS	NS
Truchuelo et al. (12) Jan 2012	1	11	1% rapamycin in Dexeryl® cream	Once daily	6 weeks	Yes	2 days	None	NS	NS	NS
Kaufman McNamara et al. (8) Feb 2012	2	21	Compounded product composed of 60 mL of rapamycin solution (1 mg ML^{-1}) and 60 g of Eucerin®	Once daily	5 months	Mild	1 month	None	NS	NS	NS
		6			3 months	Excellent					
Fosters et al. (7) Feb 2012	4	6-17	2/4 with 1% rapamycin in ointment	Twice daily	6 months	40-90%	1 week	None	NS	Yes	NS
			2/4 with commercially available oral rapamycin solution (1 mg ML^{-1})	Once daily due to local irritation		85%		2/2 local irritation			
Valerón-Almazán et al. (13) March 2012	1	27	Topical 1 mg/mL rapamycin	Twice daily	3 months	Yes	NS	None	NS	NS	NS

(to be continued)

(Continued from Table 3)

Koenig et al. (10) Sept 2012	28	>13	10/28 with placebo	Once daily	6 months	28% Yes 62% No	NS	2/28 local burning sensation	NS	NS	NS
			9/28 with 0.003% rapamycin in Skincerity®			73% Yes 27% No No statistically significant difference between high-dose and low-dose treatment					
			9/28 with 0.015% rapamycin in Skincerity®								
Salido et al. (4) Oct 2012	10	6-43	0.4% rapamycin in petrolatum	3 times a week	9 months	FASI improvement: <75%: 2/10 50-75%: 4/10 34.3-50%: 4/10 <34.3%: 0/10	4 weeks (earlier in children)	None	NS	NS	NS
Tanaka et al. (11) Dec 2013	11	2-36	4/11 with 0.2% rapamycin in gel	Twice daily	12 weeks	Yes (more rapid and better in the gel-treated group; better response in patients aged <10 years)	NS	None	NS	Yes	4 weeks
			7/11 with 0.2% rapamycin in ointment								
Tu et al. (14) Dec 2013	19	6-20	1% rapamycin (crashed tablets) in petrolatum (Jan.2011- June 2012) Since July 2012, 0.5% rapamycin powder in petrolatum	Twice daily (When clearance, reduce to thrice weekly)	8-20 months	Excellent 8/19 Good 9/19 Moderate 2/19 (perceived superiority of crashed tablets compared to powder)	2 weeks	1/19 bleeding of a FA 1/19 perioral dermatitis	One daily application for convenience		

NS: not specified

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