Use of topical rapamycin in the treatment of superficial lymphatic malformations

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Background: The superficial lymphatic component of vascular malformations poses a significant treatment challenge. It is responsible for the majority of symptoms presented, and to date, there is no consensus regarding treatment.

Objective: To evaluate the effectiveness of topical rapamycin in treating superficial lymphatic malformations (LM).

Methods: A case series study was performed of patients with superficial LM, treated with topical rapamycin. The clinical characteristics of patients and the concentration and application mode of the drug were recorded. The changes in the signs and symptoms observed and associated adverse effects were noted and analyzed.

Results: The study population consisted of 11 patients of an average age of 10.5 years. All were treated with topical rapamycin: 6 patients with a 1% concentration, 1 with a 0.8% concentration, and 4 with a 0.4% concentration. Changes in the clinical appearance of the lesions were observed in all patients. The associated symptoms, present in 9 of 11 patients, improved in every case. The mean follow-up time was 16.1 months.

Limitations: This study is retrospective, with a small sample size and considerable heterogeneity of lesions and treatment approaches.

Conclusion: Treatment with topical rapamycin modifies the clinical appearance and alleviates symptoms of superficial LM. (J Am Acad Dermatol 2019;80:508-15.)

Key words: lymphatic malformation; ointment; rapamycin; sirolimus; topical; vascular anomalies.

Lymphatic malformations (LM) are low-flow vascular malformations secondary to an abnormal development of the lymphatic system. They usually occur 6-10 weeks after gestation as a result of immature lymphatic tissue failing to connect with the venous or lymphatic system. The estimated incidence is 1 in 2000-4000 live births; there is no differences between the sexes.[1] In 50%-60% of cases, these malformations are evident at birth

Abbreviation used:
LM: lymphatic malformation

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and grow proportionally to the individual; 90% are diagnosed before the age of 2 years.[2] They might be simple or form part of combined vascular malformations (associated with capillary, arterial, or venous malformations).[3] The superficial component is characteristic of the microcystic variant, although it can be present in any subtype. The malformation usually manifests clinically in the form of small translucent agminated vesicles resembling frog spawn. Patients frequently report symptoms such as serous or bloody exudate, pruritus, pain, inflammation, or even episodes of superinfection.[4]

To date, no consensus has been reached on treatment for the superficial lymphatic component of vascular malformations. Many options are available but most present high recurrence rates (50%-66%) and frequent side effects.[5] The presence of numerous small cysts, a lack of communication between cysts, and combination with a deeper component often limit the efficacy of surgical resection and other treatments.[6] Patients have been treated by surgical resection; cryotherapy; suction lipectomy; radiotherapy; laser therapy (CO_2, argon, or pulsed dye); sclerotherapy (bleomycin, doxycycline, picibanil, and pingyangmycin); and systemic drugs, such as sildenafil.[7,8] However, none of these approaches has become accepted as a first-line treatment. Therefore, alternative treatments are needed that offer greater effectiveness and reduced morbidity.

Rapamycin has been shown to be useful in the treatment of vascular malformations with a lymphatic component when administered systemically,[9] but few reports exist in its topical use for this purpose.

CAPSULE SUMMARY

- Rapamycin can be useful in the treatment of vascular malformations, but the value of its topical application to superficial lymphatic malformations has not been established.
- Topical rapamycin improves the clinical appearance of superficial lymphatic malformations and alleviates associated symptoms.

METHOD

We conducted a case series study of patients seeking treatment for vascular malformations with a superficial lymphatic component treated with topical rapamycin at 7 different hospitals. The epidemiologic variables of patients, clinical characteristics of malformations, related symptoms, and details of previous treatments were all compiled. In addition, the concentration and excipients of the topical rapamycin preparation, application method, and duration of treatment were recorded. After treatment, changes in the clinical signs (assessed by photograph by 2 dermatologists) and symptoms of the malformations as well as side effects were noted.

RESULTS

The study population consisted of 11 cases of vascular malformations with a superficial lymphatic component, treated with topical rapamycin (Tables I and II). The average patient age was 10.5 (range 5-16) years, and there was a predominance of female patients (8:3). Eight of the lesions were microcystic LM, 2 of which had a reticulate appearance clinically, and 3 lesions were combined vascular malformations. Nine patients had associated symptoms (exudate, bleeding, pain, inflammation, or superinfection), and 2 were asymptomatic. Five patients had undergone previous treatment, with techniques including sclerotherapy (picibanil, ethoxysclerol, bleomycin), CO_2 laser therapy, pulsed dye laser therapy, cryotherapy, or electrosurgery.

In all cases, the active principle was formulated as an ointment of various concentrations. Six patients received rapamycin at 1%, 1 at 0.8%, and 4 at 0.4%. For 8 patients, the drug was initially administered twice a day, and for the other 3, once a day.

In all cases, we observed changes with the lesions, such as reduced surface area (36%), attenuation of color (72%), and decreased vesicle volume (73%) (Figs 1-6). All 9 patients who had associated symptoms improved in this respect. Seven patients reported a reduction in exudate; 4 obtained pain relief; 2 had fewer outbreaks of inflammation, and 2 indicated the elimination of superinfections. Improvement generally became apparent after 2-4 weeks of treatment, and the mean follow-up was 16.1 (range 6-24) months. The only side effect recorded was slight transient local irritation in 1 patient.

DISCUSSION

Rapamycin, also known as sirolimus, is a macrolide antibiotic that is obtained from the fermentation products of the bacterium *Streptomyces hygroscopicus*. The drug was initially used as an antifungal agent until the mid-1970s, when its immunosuppressive, antiproliferative, and anti-angiogenic properties in humans were discovered. In the 1990s, it was found that these properties originated from its inhibitory effect on mTOR. The rapamycin molecule is a serine-threonine

kinase that regulates the of phosphatidylinositol-3-kinase—Akt signaling pathway.[10,11] The drug acts, therefore, as a master key in various catabolic, anabolic, and other processes related to cell mortality, angiogenesis, and cell growth. Rapamycin blocks endothelial differentiation and vascular repair mediated by pluripotent cells, prevents the accumulation of hypoxia-inducible factor-1a, which stimulates angiogenesis secondary to hypoxia, blocks vascular endothelial growth factor signaling, and influences wound healing by modulating vascular filtering and dermal edema.[12]

In view of these multiple properties, rapamycin has been used in diverse ways, beyond the original oral application, to treat diverse vascular malformations, including those with lymphatic components. Hammill et al described 5 patients with diffuse microcystic LM with pleural involvement and frequent episodes of chylothorax treated satisfactorily with rapamycin.[9] Also, Alemi et al reported 2 patients with microcystic LM with airway obstruction that improved significantly after treatment with rapamycin.[13] Two cases of lingual LM[14,15] and a case of central conducting lymphatic anomaly[16] have been described for which good treatment response with rapamycin was achieved. Other conditions such as lymphangiomatosis and lymphangioleiomyomatosis have also shown satisfactory responses to the drug.[17-19] A phase 2 clinical trial conducted by Adams et al included patients with microcystic LM or combined vascular malformations, and partial responses were obtained in most cases.[20] Strychowsky et al recently published 19 cases of refractory cervicofacial LM, in which the volume of the malformation decreased in all patients treated with oral rapamycin.[21] However, oral rapamycin drug delivery requires periodic analytical studies to determine its levels in the blood, and this treatment is not free of complications, such as headache, mucositis, hypercholesterolemia, and elevation of liver enzymes.[9] In the case of oral delivery, the concomitant administration of prophylactic antibiotics is advisable to combat the risks for neutropenia and opportunistic infections.[22]

Despite the potential value of rapamycin in the treatment of LM, its topical use for this purpose is not well known. Although administering the drug topically limits its effectiveness to the area of application, rapamycin can be useful for treating lesions with a superficial lymphatic component. The literature contains many references indicating the effectiveness of topical rapamycin in the treatment of cutaneous manifestations of the tuberous sclerosis complex, with good results and a high safety profile.[23,24] Its effectiveness has also been documented

Table I. Descriptive analysis of patients treated with topical rapamycin ointment

Variable	Total, n/total	%
Total	11	100
Mean age, years	10.5	
Sex		
Male	3/11	27
Female	8/11	73
Malformation		
MLM	6/11	55
RMLM	2/11	18
CLM	1/11	9
MVLM	1/11	9
VLM	1/11	9
Concentration, %		
1	6/11	55
0.8	1/11	9
0.4	4/11	36
Frequency		
Once daily	3/11	27
Twice daily	8/11	73
Decrease in signs	11/11	100
Surface area of lesion	4/11	36
Vesicle volume	8/11	73
Vesicle color	8/11	72
Decrease in symptoms	9/9	100
Pain	4/9	44
Exudate	7/9	78
Inflammation	2/9	22
Superinfection	2/9	22
Side effects	1	9
Local irritation	1	9
Follow-up, mon	16.1	

CLM, Capillary lymphatic malformation; *MLM*, microcystic lymphatic malformation; *MVLM*, microcystic veno-lymphatic malformation; *RMLM*, reticulate microcystic lymphatic malformation; *VLM*, veno-lymphatic malformation.

in a patient with symptomatic tufted angioma not associated with coagulopathy and also (in combination with pulsed-dye laser therapy) in patients with capillary malformations.[25,26] With respect to the efficacy of topical sirolimus for microcystic LM, to our knowledge, 6 cases have been previously reported (2 of which were reported herein updated as cases 3 and 4), all of which had a good response to sirolimus 0.3%-1% ointment or 0.1% solution.[27-29]

In the present study, a favorable response was observed in the clinical signs of disease (surface area, color, and volume of vesicles) in all patients, although the changes were not always of the same type or intensity. All patients initially having symptoms (9 of 11) obtained marked improvements. Exudate, a characteristic symptom of this type of lesion, was notably alleviated in all the patients in whom it was present. Patients 2, 3, and 4, who had

Table II. Epidemiologic and clinical characteristics of patients treated with topical rapamycin ointment

Patient no.	Sex/age, y	Lesion	Site	Symptoms	Previous treatment	Ointment concentration, %	No. applications per day	Change in signs	Change in symptoms	Follow-up, mon
1	M/8	VLM	Right hip	Exudate	Sclerotherapy with ethoxysclerol, PDL	1	2	Color attenuation	Reduced exudate	7
2	F/6	MLM	Right arm	Exudate	No	1	2	Color attenuation, reduced surface area, reduced vesicle volume	Reduced exudate	12
3	M/5	MLM	Right buttock	Exudate, superinfection	Sclerotherapy with bleomycin, PDL	1	1	Color attenuation, reduced surface area, reduced vesicle volume	Reduced exudate, fewer episodes of superinfection	24
4*	F/13	MLM	Right buttock	Exudate, superinfection, inflammation, pain	Cryotherapy	1	2	Color attenuation, reduced vesicle volume	Reduced exudate; fewer episodes of superinfection, inflammation, and pain	24
5	F/10	MLM	Right inframammary	Inflammation, pain	CO_2 laser therapy	1	2	Reduced vesicle volume	Fewer episodes of inflammation and pain	15
6	F/8	MVLM	Right inframammary	Exudate, pain	No	1	2	Color attenuation, reduced vesicle volume	Reduced exudate, fewer episodes of and pain	13
7†	F/16	MLM	Right scapular	Exudate	No	0.8	1	Color attenuation, reduced surface area, reduced vesicle volume	Reduced exudate	24
8‡	F/14	RMLM	Posterior cervical	-	No	0.4	1	Color attenuation	-	18
9	M/12	CLM	Right thigh	Pain	No	0.4	2	Reduced vesicle volume	Fewer episodes of and pain	10
10	F/13	MLM	Right inframammary	Exudate	Sclerotherapy with picibanil, cryotherapy, electrosurgery	0.4	2	Reduced vesicle volume	Reduced exudate	6
11§	F/11	RMLM	Left shoulder	-	No	0.4	1	Color attenuation, reduced surface area	-	24

CLM, Capillary lymphatic malformation; *MLM*, microcystic lymphatic malformation; *MVLM*, microcystic venolymphatic malformation; *PDL*, pulsed dye laser; *RMLM*, reticulate microcystic lymphatic malformation; *VLM*, venolymphatic malformation.

*Application was reduced to once every 2 days and the effectiveness was maintained.

†Initial session with CO_2 laser therapy. Two weeks later, treatment with 0.8% topical rapamycin was started. Application was reduced to once every 2 days, and the effectiveness was maintained.

‡Increased to 2% in the final 6 months of follow-up, with no change.

§After 3 months at 0.1% with no improvement, the concentration was increased to 0.4%, which led to a favorable response.

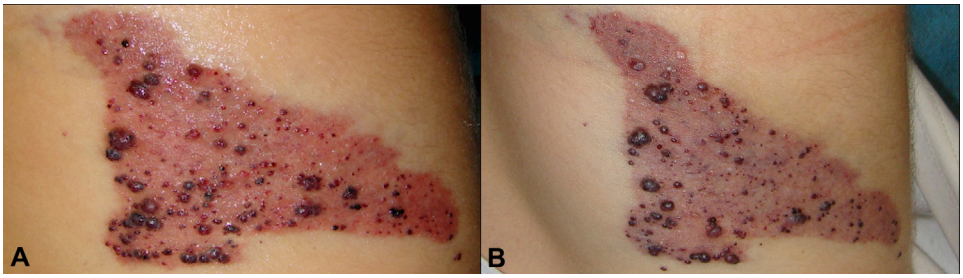

Fig 1. Patient 1 before (**A**) and after (**B**) 7 months of treatment. Changes were seen in the color and volume of the vesicles.

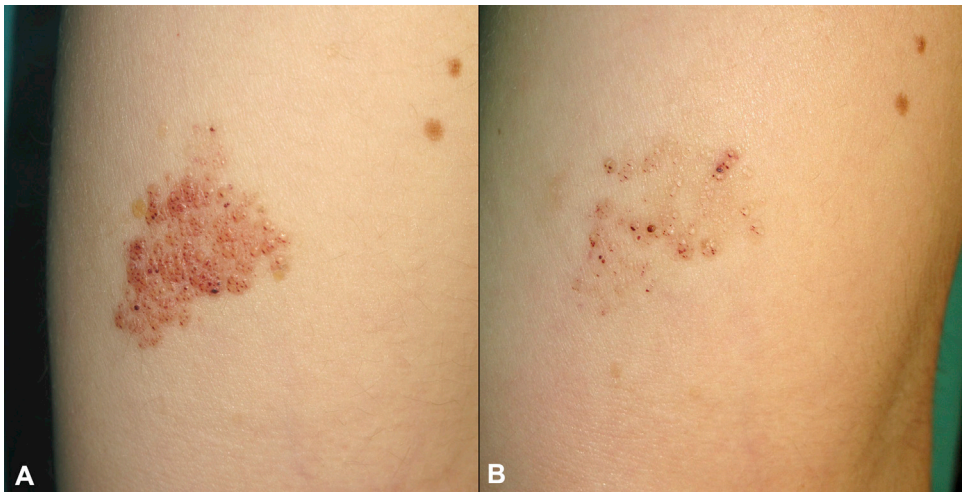

Fig 2. Patient 2 before (**A**) and after (**B**) 1 year of treatment. A reduction in the surface area and volume of vesicles was seen, along with attenuation of color.

microcystic LM and were treated with 1% rapamycin, obtained the highest degree of overall improvement. Patient 7, who was treated with 0.8% rapamycin, initially received a CO_2 laser session, which helped reduce the volume of the vesicles. The improvement was sustained over time, in contrast with the usual outcome that occurs when this therapy is administered alone. It seems, therefore, that combined treatment of topical rapamycin with laser therapy ($C0_2$ or pulsed dye) could heighten the effectiveness of topical treatment alone and avoid the recurrences normally associated with laser therapy.[30] The 2 patients in our group with reticulate LM both received the same concentration of rapamycin and treatment regimen, but in 1 case, the clinical signs improved notably, and in the other, only a slight alleviation was observed.

The heterogeneity of the sample in terms of the type of lesion, the concentration of drug (0.4%-1%), and the number of applications applied prevents us from drawing firm conclusions about which particular characteristics are associated with a more favorable overall response. However, it seems evident that the concentration should be >0.1%, which is the level usually used in treating angiofibromas of the tuberous sclerosis complex.[24] Among our patients, 0.1% rapamycin ointment was used for 3 months in patient 11 without achieving any objective response, which is why the concentration was then increased to 0.4%, producing a significant improvement.

It should be noted that the treatment described herein is not expected to be curative. The main goal with these patients is to achieve the optimal control of symptoms. After doing so, the minimum effective dose should be used because this treatment must be maintained over time; patients who temporarily suspended treatment experienced relapses. For this reason, for patients 4 and 7, the frequency of application was reduced to once every 2 days, with which a satisfactory response was maintained. Regarding its deep-level effectiveness, neither imaging nor histologic studies have been performed in any of the patients to reveal the impact of the drug in this respect. Because topical application obtains only limited penetration, we would expect the rapamycin ointment to perform relatively poorly at deeper

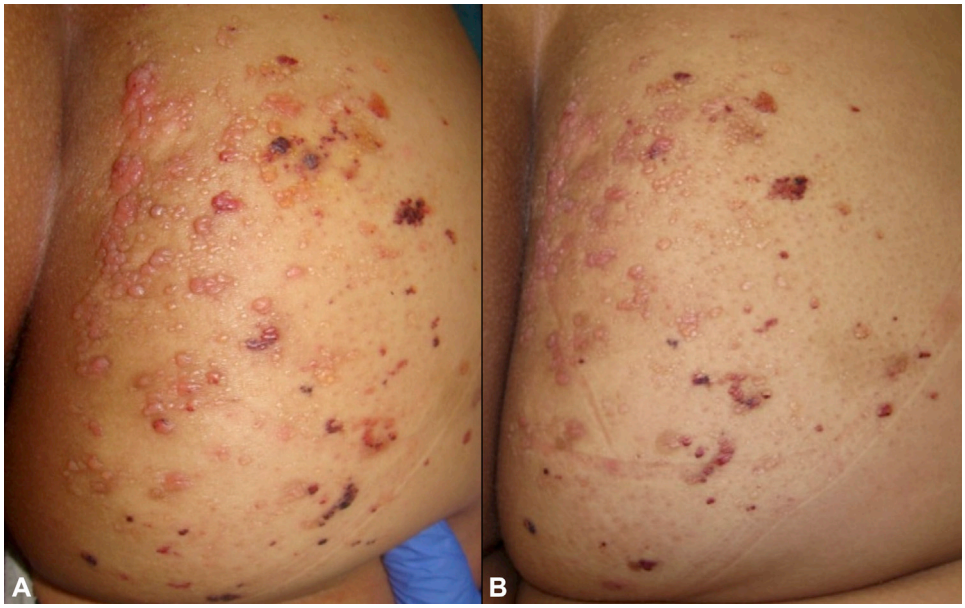

Fig 3. Patient 4 before (**A**) and after (**B**) 12 months of treatment. A decrease in the volume of the larger vesicles and attenuation of color were seen.

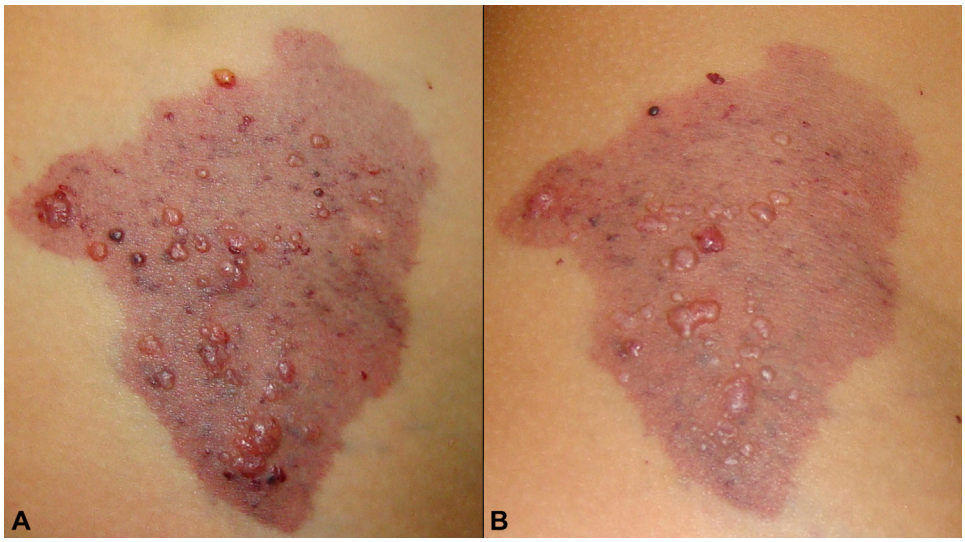

Fig 4. Patient 6 before (**A**) and after (**B**) 10 months of treatment. A slight decrease in the volume of vesicles was seen.

levels. As expected, no overall clinical change was observed in the deeper lymphatic component of lesions treated with topical rapamycin.

Many current treatments for the surface component of LM (eg, cryotherapy and pulsed dye laser therapy) are painful, and others require local or even general anaesthesia.[8] Moreover, in many cases, a prolonged recovery time is required. Topical rapamycin, on the other hand, is well tolerated, which is of considerable importance because in many cases the symptoms of these lesions begin in early childhood. The only notable side effect in our patients was transient local irritation in 1 case. This finding is in accordance with what has been described previously concerning other pathologies, although a recent report mentioned the appearance of allergic contact dermatitis in a patient with a capillary malformation treated with laser therapy and topical rapamycin.[31] Regarding the risk for systemic absorption of the drug, blood levels were not determined in any of the cases considered. Although additional studies are needed regarding the potential for systemic absorption of topical rapamycin, in a series of patients treated topically with concentrations of up

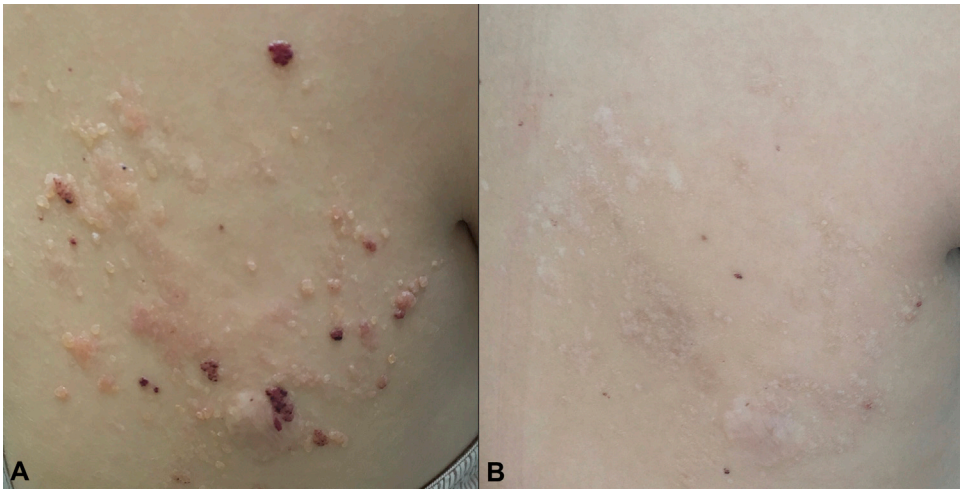

Fig 5. Patient 7 before (**A**) and after (**B**) 1 year of treatment. Initial session involved CO_2 laser therapy and complementary treatment with topical rapamycin (started 2 weeks after conclusion of laser treatment). During follow-up of topical treatment, no new vesicles appeared.

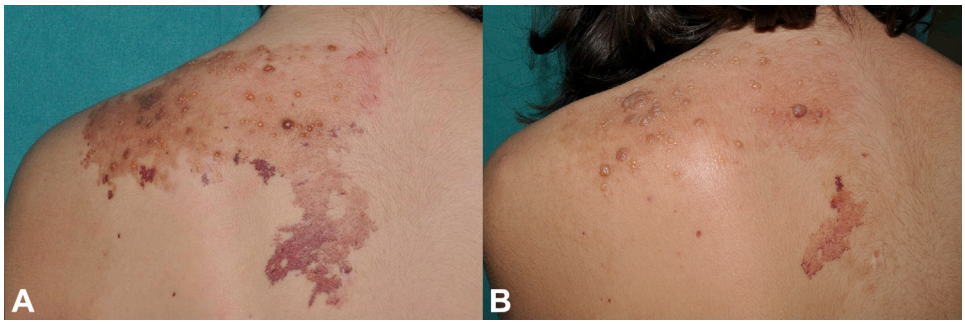

Fig 6. Patient 11 before (**A**) and after (**B**) 8 months of treatment. A considerable reduction in the surface area of the lesion was seen, along with marked attenuation of color.

to 8% for psoriasis, 1% for facial angiofibromas (with other occasional reports of low detectable levels, ≤0.8 ng/mL), and 0.1%-0.3% for vascular malformations, the levels in the blood were undetectable.[29,32,33] Furthermore, no symptoms related to systemic absorption have been detected in any case.

With respect to the preparation of the drug for topical application, it should be noted that rapamycin is a hydrophobic compound that must be formulated in an oily excipient.[34] Nevertheless, optimum stability of the drug is readily obtained because it is occlusive and practically anhydrous.

The case series design and retrospective nature of this study can be considered study limitations. In addition, the clinical characteristics of the patients and of the treatment regimens varied considerably, which prevents us from drawing firm conclusions.

CONCLUSION

We present a series of patients with superficial LM successfully treated with topical rapamycin. The treatment response obtained, in terms of clinical signs and symptoms, was satisfactory in every case, with a good safety profile. The minimum effective concentration was found to be 0.4%, applied at least once a day. Once symptoms are controlled, the drug might be applied less frequently, according to the individual's pattern of response. Currently, there is no first-line treatment known to be both effective and free of side effects for this pathology. The results obtained in our study show that topical rapamycin could be a valuable alternative for the treatment of superficial LM, although further research with a higher level of evidence should be conducted to establish solid recommendations for clinical practice.

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