ORIGINAL ARTICLE

Long-term treatment of cutaneous manifestations of tuberous sclerosis complex with topical 1% sirolimus cream: A prospective study of 25 patients

Nausicaa Malissen, MD,[a] Laurence Vergely, PharmD,[b] Marguerite Simon, PharmD,[b] Agathe Roubertie, MD, PhD,[c] Marie-Claire Malinge, MD,[d] and Didier Bessis, MD[a,e,f]
Montpellier and Angers, France

Background: Data on long-term topical sirolimus treatment of the cutaneous manifestations of tuberous sclerosis complex are rare.

Objective: To evaluate the long-term benefit and tolerance of topical 1% sirolimus in tuberous sclerosis complex.

Methods: In this 18-month prospective single-center study, 1% sirolimus cream was applied daily to facial angiofibromas (FAs), fibrous cephalic plaques (FCPs), shagreen patches, hypomelanotic macules, and ungual fibromas. After complete clearance (CC) of FAs, we evaluated a maintenance protocol of 3 applications weekly.

Results: Twenty-five patients were enrolled. Fifty percent obtained CC of FAs within 9 months. Of 7 patients with CC (58%) who were following the maintenance protocol, 6 relapsed within 7 months and 1 was still responding at 1 year. Of 16 patients with FCPs, 7 (44%) remained stable at 12 months and 9 (56%) improved after 3 to 9 months of treatment. Only 1 of 5 patients treated for shagreen patches showed improvement at 12 months. Treatment was well tolerated with no serious adverse events.

Limitations: The small number of patients was a limitation.

Conclusions: Topical 1% sirolimus applied daily produced positive responses in treatment of FAs, FCPs, and facial hypomelanotic macules and was well tolerated. A 3-times-weekly maintenance protocol did not prevent FA relapses. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2017.04.005.)

Key words: angiofibromas; fibrous cephalic plaque; hypomelanotic macules; shagreen patch; sirolimus; treatment; tuberous sclerosis complex; ungual fibroma.

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder caused by mutations in the tuberous sclerosis 1 *(TSC1)* or tuberous sclerosis 2 (*TSC2*) suppressor genes, which encode the hamartin and tuberin proteins, respectively.[1,2] Physiologically, those 2 proteins interact as a complex and down-regulate the mammalian target of the rapamycin signaling pathway involved in the control of cell proliferation and growth.[3]

Cutaneous manifestations in patients with TSC include, in decreasing order of frequency,

From the Department of Dermatology, Saint-Eloi Hospital and Montpellier University Hospital[a]; Department of Clinical Pharmacy and Oncology, Lapeyronie Hospital, Montpellier[b]; Department of Neuropediatric and Regional Center of Competence of Tuberous Sclerosis, Gui de Chauliac Hospital, Montpellier[c]; Department of Molecular Genetics, Angers University Hospital[d]; Institut National de la Santé et de la Recherche Médicale (INSERM) U1058, Montpellier[e]; and Regional Center of Competence for Rare Skin Disorders, Montpellier.[f]

Funding sources: None.

Conflicts of interest: None declared.

Accepted for publication April 5, 2017.

Reprint requests: Didier Bessis, MD, Department of Dermatology, Saint-Eloi Hospital, CHU Montpellier, 80, avenue Augustin Fliche, 34295 Montpellier cedex, France. E-mail: didierbessis@gmail.com.

Published online May 11, 2017.

0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2017.04.005

hypomelanotic macules, angiofibromas or fibrous cephalic plaques (FCPs) (*forehead plaques* in older terminology), ungual fibromas, and shagreen patches.[4,5] Facial angiofibromas (FAs), FCPs, and facial hypomelanotic macules can cause disfigurement or stigmatization and thereby have an impact on quality of life.[6]

Since 2010, several studies (with patients totaling 123) have reported that topical sirolimus is a useful treatment for the FAs of TSC (Supplemental Table I; available at http://www.jaad.org).[7-25] Rare or no data are available on topical sirolimus for treating FCPs,[12,14,18] hypomelanotic macules,[12,25,26] ungual fibromas,[27] or shagreen patches. The short median period of follow-up in these reports (4 months) precludes predictions about the duration of treatment needed to obtain a complete response and the relapse risk when sirolimus application is reduced.

We evaluated longer-term application of 1% sirolimus cream to the cutaneous manifestations of TSC, including FAs, FCPs, shagreen patches, ungual fibromas, and hypomelanotic macules. Our secondary objective was to assess the benefit of a maintenance protocol for FAs and the long-term tolerance of treatment.

CAPSULE SUMMARY

- Information is limited on long-term use of topical sirolimus for the cutaneous manifestations of tuberous sclerosis complex.
- Long-term topical 1% sirolimus treatment appears to benefit facial angiofibromas, fibrous cephalic plaques, and facial hypomelanotic macules.
- Topical 1% sirolimus could be a therapeutic alternative to laser treatment or surgery for the facial cutaneous lesions of tuberous sclerosis complex.

MATERIAL AND METHODS

Study design

From June 2015 to December 2016, we prospectively included all patients who requested and received topical sirolimus treatment for TSC skin manifestations at the Regional Center of Competence of Tuberous Sclerosis Complex of the University Hospital of Montpellier. Our local ethics committee approved the study protocol (IRB 15/06.06, dated June 9, 2015).

Inclusion criteria

Eligible patients were consecutively included if they had a diagnosis of TSC based on validated criteria[5] from the 2012 International Tuberous Sclerosis Complex Consensus Group and agreed to use contraception or avoid pregnancy, if relevant. Patients, or parents of patients younger than 18 years, had to have the ability to understand the study and its risks, side effects, and potential benefits and agree to an 18-month study that would include monthly clinical, photographic, and (for the first 2 months) biologic evaluations. Exclusion criteria were having taken oral mammalian target of rapamycin inhibitors within the past 12 months, having missed 1 of the first 2 evaluations, or having a treatment compliance rate less than 50%.

Drug formulation

The cream was prepared from sirolimus powder (INRESA Pharma, Bartenheim, France) by the Central Pharmacy of the University Hospital of Montpellier. An emollient cream, Dexeryl (Pierre Fabre Medicament, Boulogne, France), containing glycerol 15%, liquid and soft paraffin 10%, glycerol monostearate, stearic acid, polydimethylcyclosiloxane, silicone oil, macrogol 600, trolamine, propyl parahydroxybenzoate, and purified water, was chosen because of its good tolerability profile[28,29] and low price. Thirty and 50 grams of 1% sirolimus cream cost 341.93 and 529.01 euros, respectively, which included the cost of the powder and emollient and the pharmacy technician's preparation time.

Treatment protocol

During the initial treatment phase, topical 1% sirolimus was applied to skin lesions once a day in the evening, in a thin layer. The proposed monthly dose for treating FAs of the cheeks, nose, and chin was 30 g, and it was increased to 50 g for supplementary treatment of hypomelanotic macules, FCPs, and/or shagreen patches. For ungual fibromas, topical sirolimus was applied daily on the periungual and/or subungual areas without occlusion. Systematic facial application of sunscreen with a sun protection factor greater than 50 in the morning was advised. In cases of complete clearance (CC) of the FAs (see later), a maintenance protocol was proposed, with the application frequency reduced to 3 times per week. The incidence of adverse events was assessed monthly by medical history and clinical examination, with analysis of blood sirolimus concentration and blood cell counts after 1 and 2 months of treatment.

Evaluation criteria

Age, sex, associated conditions, and physical features, including cutaneous features and brain,