Dermatol Ther (Heidelb) (2023) 13:1113–1126
https://doi.org/10.1007/s13555-023-00914-2

ORIGINAL RESEARCH

Topical Sirolimus 0.2% Gel for the Management of Tuberous Sclerosis Complex-Related Cutaneous Manifestations: An Interim Analysis of Postmarketing Surveillance in Japan

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Received: October 28, 2022 / Accepted: February 23, 2023 / Published online: March 11, 2023

ABSTRACT

Introduction: Tuberous sclerosis complex (TSC) is a rare autosomal dominant genetic disorder affecting several organs, including skin. We sought to assess the real-world effectiveness and safety of a topical sirolimus 0.2% gel treatment for TSC-related cutaneous manifestations.

Methods: We conducted an interim analysis of postmarketing surveillance conducted in Japan over 52 weeks. A total of 635 and 630 patients were included in the safety and efficacy analysis sets, respectively. Improvement rate of overall cutaneous manifestations, responder rate of improvement in individual lesions, adverse events (AEs), adverse drug reactions (ADRs), and patient satisfaction level of topical sirolimus 0.2% gel treatment were evaluated along with patient characteristics associated with the improvement rate of cutaneous manifestations or safety.

Results: The mean age of the patients was 22.9 years and 46.1% were men. At week 52 of treatment, the overall improvement rate was 74.8% and the responder rate was the highest for facial angiofibroma (86.2%). Overall, the incidence rates of AEs and ADRs were 24.6% and 18.4%, respectively. Efficacy was associated with age (< 15, ≥ 15 to < 65, and ≥ 65 years, $p = 0.010$), duration of use ($p < 0.001$), and total dosage ($p = 0.005$). Safety was associated with age (< 15, ≥ 15 to < 65, and ≥ 65 years, $p = 0.011$) and duration of use ($p < 0.001$). However, when the broad age group (≥ 15 to < 65) was subcategorized by 10-year intervals, the incidence of ADRs was similar among the age groups with no significant differences. Hepatic or renal impairment or concomitant use of systemic mTOR inhibitors had no effect on the effectiveness or safety. Overall, 53% of patients were "very satisfied" or "satisfied" with the treatment received.

Conclusions: Topical sirolimus 0.2% gel is effective in the management of TSC-related cutaneous manifestations and generally well tolerated. Age and duration of usage had a significant association with the effectiveness or

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13555-023-00914-2.

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safety of topical sirolimus 0.2% gel, whereas total dosage had a significant association with the effectiveness.

Keywords: Angiofibroma; Effectiveness; Adverse events; Adverse drug reactions; Mechanistic target of rapamycin inhibitors; Patient satisfaction; Postmarketing surveillance; Sirolimus topical; Tuberous sclerosis complex

Key Summary Points

Why carry out this study?

This postmarketing survey was conducted in compliance with the Good Postmarketing Study Practice ordinance of the Ministry of Health, Labor and Welfare (MHLW).

To date, this is the first real-world experience of the topical mechanistic target of rapamycin (mTOR) inhibitor sirolimus 0.2% gel (Rapalimus®, Nobelpharma Co., Ltd., Tokyo, Japan) for tuberous sclerosis complex (TSC)-related cutaneous manifestations over 52 weeks of treatment.

What was learned from the study?

In this postmarketing surveillance, the improvement in the overall cutaneous manifestations with topical sirolimus 0.2% gel treatment at 52 weeks was 74.8%.

The overall incidence rate of adverse events (AEs) and adverse drug reactions (ADRs) was 24.6% and 18.4%, respectively.

Age and duration of use showed a significant association with both effectiveness and safety, whereas total dosage showed significant association with effectiveness.

Topical sirolimus 0.2% gel may be useful in the management of TSC-related cutaneous manifestations.

INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant rare genetic disorder that affects one in every 6000–10,000 live births globally [1–3]. TSC is caused by loss-of-function mutations in either *TSC1* or *TSC2* genes, which encode hamartin and tuberin, respectively, that inhibit the tumor-suppressive activity of the mechanistic target of rapamycin (mTOR), affecting various organs including the skin, central nervous system, eyes, heart, lungs, and kidneys [1–3]. Cutaneous manifestations such as hypomelanotic macules, facial angiofibroma, periungual fibromas, shagreen patches, fibrous cephalic plaque, and confetti skin lesions affect more than 90% of patients [4, 5].

Pharmacological (topical or oral mTOR inhibitors) and non-pharmacological (surgical or excision) treatment options are available for the treatment of TSC cutaneous symptoms [3]. The use of topical mTOR inhibitors provides a painless, non-scarring option, while oral mTOR inhibitors typically show improvement in the skin condition of patients. According to the most recent international TSC guidelines, mTOR inhibitors can be appropriate therapeutic options for large or disfiguring lesions as well as painful lesions or those prone to bleeding [3]. Although the use of systemic mTOR inhibitors for other indications showed improvement in the skin condition of patients [3], the risk–benefit ratio often precludes their use for TSC cutaneous manifestations alone. Subsequently, topical sirolimus was suggested as a safe and effective approach for treating facial angiofibroma [3]. The efficacy and safety of topical sirolimus 0.2% gel in the management of facial angiofibroma and other cutaneous manifestations were established [6–8]. The gel was approved in Japan in 2018 for the treatment of TSC-related cutaneous lesions, and recently approved in the USA (HYFTOR™) for the treatment of facial angiofibroma. In this article, we present the findings of interim analyses of postmarketing surveillance (PMS) conducted in Japan aimed to better understand the real-world effectiveness and safety of topical sirolimus 0.2% gel for the management of TSC-related

cutaneous manifestations. In addition, the demographics and baseline patient characteristics associated with the efficacy and safety of topical sirolimus 0.2% gel for treating TSC-related manifestations were analyzed.

METHODS

Study Design and Participants

The general drug use survey of topical sirolimus 0.2% gel (Rapalimus®, Nobelpharma Co., Ltd., Tokyo, Japan) is an ongoing multicenter PMS in Japan for the treatment of TSC-related cutaneous manifestations. The diagnosis of TSC was based on the diagnostic criteria in the Japanese guidelines, modified TSC Clinical Consensus Conference 2012 criteria [1, 3]. Data were collected on patient background factors such as age, gender, height, weight, time of onset of symptoms, time of acquiring a definite diagnosis, clinical symptoms of TSC, allergy history, medical history, complications, and prior treatment. During a routine medical check-up, data on symptom evaluation were collected.

This PMS was conducted in compliance with the Good Postmarketing Study Practice (GPSP) ordinance of the Ministry of Health, Labor and Welfare (MHLW). MHLW approval was subject to all patients using the medication being monitored. According to the MHLW's GPSP ordinance, the study's entire protocol does not need to receive approval from an ethical committee. Informed consent was not required under GPSP.

Effectiveness Evaluation

Improvement in the overall cutaneous manifestations with the use of topical sirolimus 0.2% gel was evaluated by physician at 52 weeks after the treatment initiation or at the time of withdrawal/dropout using the following seven-point scale: "markedly improved," "improved," "somewhat improved," "unchanged," "somewhat worsened," "worsened," or "not evaluable." The proportion of patients who were rated as "markedly improved" or "improved" to the total number of patients evaluated is defined as the "improvement rate." The relationship between demographics and baseline characteristics and the improvement rate was analyzed. Improvement in individual lesions, facial angiofibroma, hypomelanotic macules, shagreen patches, fibrous plaque, and periungual fibroma was graded by physician on a three-point scale as "improved," "unchanged," or "worsened" at 4, 12, 26, 38, and 52 weeks after initiating topical sirolimus 0.2% gel or at the time of withdrawal/dropout. The proportion of patients who were evaluated as "improved" to the total number of patients evaluated is defined as the "responder rate."

Safety Evaluation

Adverse events (AEs) occurring during the first 52 weeks after initiating topical sirolimus 0.2% gel treatment or within 28 days after discontinuing the therapy were investigated. AEs and adverse drug reactions (ADRs; events for which the causal relationship with this drug could not be ruled out) were classified by preferred term and system organ class according to the Medical Dictionary for Regulatory Activities/Japanese version MedDRA/J ver. 23.1. The relationship between demographics and baseline characteristics and the ADR incidence rate was analyzed.

Patient Satisfaction Level

The patient satisfaction level with topical sirolimus gel 0.2% treatment was recorded and graded on the following seven-point scale: "very satisfied," "satisfied," "somewhat satisfied," "neither satisfied nor dissatisfied," "somewhat dissatisfied," and "not evaluable."

Statistical Analysis

Descriptive statistics are presented for the demographics and baseline characteristics. The categorical variables are presented as numbers and frequencies, whereas continuous variables were presented as mean and standard deviation. For improvement rates two-sided 95% confidence intervals (CI) were estimated. The

association of demographics and baseline characteristics with the effectiveness and safety of topical sirolimus 0.2% gel was analyzed using chi-squared tests for nominal data and the Cochran–Armitage trend test for ordinal data. The two-sided level of significance was set at 0.05. Statistical analysis was performed using SAS 9.4 software.

RESULTS

Participants

In this multicenter PMS, 866 patients were enrolled from 388 sites (305 centers) across Japan. Of the 670 patients whose forms were available, 35 patients were excluded (32 patients were lost to follow-up and 3 patients were without drug administration) and 635 patients were included in the safety analysis. For the effectiveness analysis, 630 patients were included, excluding five patients because of off-label use (the use for suppression of recurrence after pulse laser treatment of simple hemangioma in three patients, the use for nevus sebaceous in one patient, and the use for eccrine poroma in one patient). The patients' disposition is presented in Fig. 1.

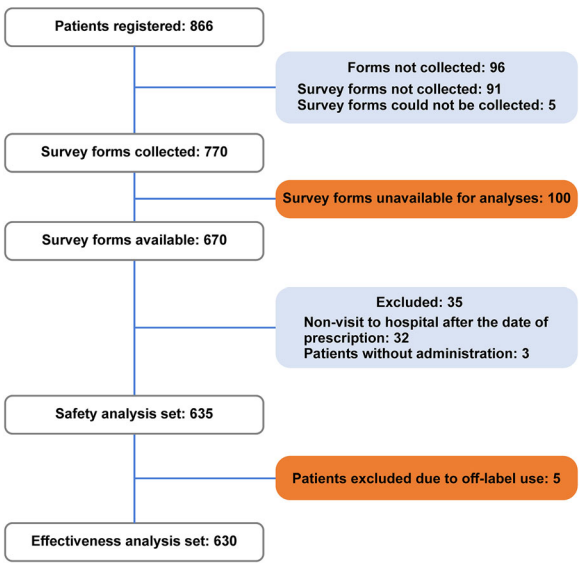


Fig. 1 Patient disposition

Demographics

The demographics and baseline characteristics of the patients included in the efficacy and safety analysis sets are presented in Table 1. The patients' mean age was 22.9 ± 14.3 years, with 53.9% of them being female. In the overall population, incidence of intellectual disability was 53.9%, renal impairment was 12.6%, hepatic impairment was 2.7%, and epilepsy was 67.9% at baseline.

Discontinuation of Topical Sirolimus 0.2% Gel

Overall, 174 patients (27.4%) discontinued topical sirolimus 0.2% gel treatment or dropped out within 52 weeks of its initiation for one or more reasons, with 38 patients (21.8%) discontinuing the drug because of AEs. Other reasons for discontinuation include personal reasons such as self-discontinuation and refusal of administration (31.0%), transfer to another hospital (21.3%), completion of treatment (15.5%), inadequate response (13.2%), and death (1.1%). Approximately 1.6%, 8.4%, 9.0%, 4.6%, and 3.9% of patients discontinued or dropped out at 0–4, 4–12, 12–26, 26–38, and 38–52 weeks, respectively.

Effectiveness of Topical Sirolimus 0.2% Gel on Overall Cutaneous Manifestations

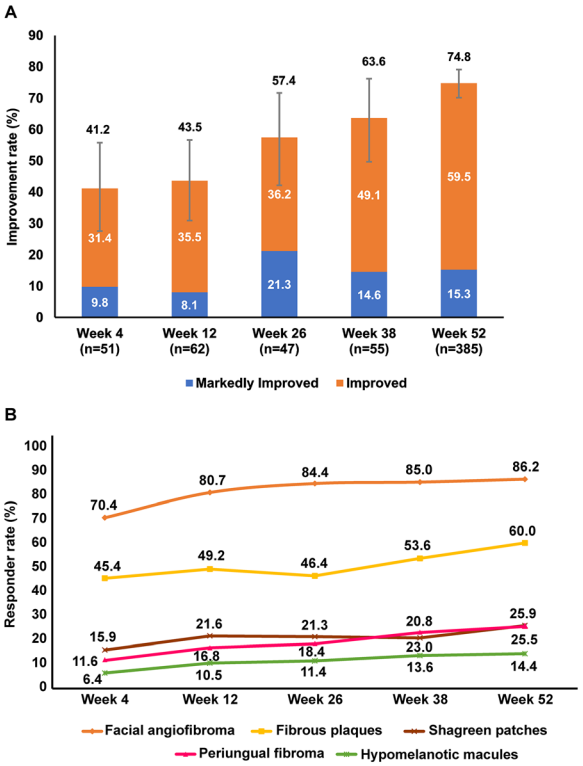
The overall improvement rate for topical sirolimus 0.2% gel over a 52-week period was 74.8% (95% CI – 70.2, 79.1), with 59 patients (15.3%) rated as "markedly improved" and 229 patients (59.5%) rated as "improved." The effectiveness increased steadily over time, rising from 41.2% (95% CI – 27.6, 55.8) at week 4 to 74.8% (95% CI – 70.2, 79.1) at week 52. Figure 2a presents the improvement rate of topical sirolimus 0.2% gel at various time points.

Table 1 Demographics and baseline characteristics of the patients included in the efficacy and safety analysis sets

Patients' background factors	Efficacy analysis (n = 630), n (%)	Safety analysis (n = 635), n (%)
Gender		
Male	292 (46.3)	293 (46.1)
Female	338 (53.7)	342 (53.9)
Age (years)		
Mean ± SD	22.9 ± 14.32	22.9 ± 14.34
< 15 years	200 (31.7)	203 (32.0)
≥ 15 to < 65 years	423 (67.1)	425 (66.9)
≥ 65 years	7 (1.1)	7 (1.1)
Inpatient/outpatient		
Inpatient	13 (2.1)	13 (2.0)
Outpatient	617 (97.9)	622 (98.0)
Duration of illness* (years)		
Mean ± SD	207.3 ± 156.37	206.9 ± 156.26
< 3 years	29 (4.6)	29 (4.6)
≥ 3 to < 5 years	18 (2.9)	18 (2.8)
≥ 5 to < 10 years	57 (9.0)	58 (9.1)
≥ 10 to < 20 years	75 (11.9)	75 (11.8)
≥ 20 years	109 (17.3)	109 (17.2)
Presence of allergy history/allergens*	69 (11.0)	69 (10.9)
Presence of medical history*	106 (16.8)	107 (16.9)
Presence of comorbidities*	540 (85.7)	542 (85.4)
Comorbidity		
Epilepsy	430 (68.3)	431 (67.9)
Intellectual disability	341 (54.1)	342 (53.9)
Renal impairment	80 (12.7)	80 (12.6)
Hepatic impairment	17 (2.7)	17 (2.7)
Others	245 (38.9)	247 (38.9)
Presence of prior treatment*	253 (40.2)	254 (40.0)
Prior treatment		
Sirolimus (topical)	46 (7.3)	46 (7.2)
Non-sirolimus drugs	222 (35.2)	223 (35.1)

SD standard deviation

*Remaining was either absent or unknown/undescribed



(n/N)	Facial angiofibroma	Fibrous plaques	Shagreen patches	Periungual fibroma	Hypomelanotic macules
Week 4	283/402	54/119	23/145	13/112	14/220
Week 12	351/435	59/120	32/148	18/1071	23/219
Week 26	341/404	51/110	29/136	9/103	21/185
Week 38	294/346	52/97	26/125	20/87	23/169
Week 52	337/391	72/120	36/139	25/98	28/195

Fig. 2 Effectiveness of topical sirolimus 0.2% gel. **a** Total improvement rate (N = 600) and **b** responder rate of the individual cutaneous manifestations

Effectiveness of Topical Sirolimus 0.2% Gel on Individual Lesions

Facial angiofibroma, hypomelanotic macules, shagreen patches, fibrous plaque, and periungual fibroma was observed in 596, 303, 209, 163, and 157 patients, respectively. Responder rates of improvement in the individual lesions at week 52 were 86.2%, 14.4%, 25.9%, 60%, and 25.5% of patients, respectively. Figure 2b presents the responder rate of the individual lesions at various time points.

Table 2 Safety profile of topical sirolimus 0.2% gel treatment (N = 635)

	Adverse events, N (%)[a]	Serious adverse events, N (%)
Patients with AEs	156 (24.6)	15 (2.4)
AEs; *n*	217	17
Skin and subcutaneous tissue disorders	89 (14.0)	0.0
Infections and infestations	12 (1.9)	1 (0.2)
Nervous system disorders	9 (1.4)	7 (1.1)
Respiratory, thoracic, and mediastinal disorders	8 (1.3)	2 (0.3)
Gastrointestinal disorders	8 (1.3)	0.0
Acne	30 (4.7)	0.0
Acneiform dermatitis	9 (1.4)	0.0
Dry skin	14 (2.2)	0.0
Skin irritation	7 (1.1)	0.0
General disorders and administration site conditions	42 (6.6)	1 (0.2)
Application site erythema	10 (1.6)	0.0
Application site irritation	18 (2.8)	0.0
Patients with ADRs	117 (18.4)	1 (0.2)
ADRs; *n*	146	1
Acne	25 (3.9)	0.0
Application site irritation	18 (2.8)	0.0
Dry skin	14 (2.2)	0.0
Application site erythema	10 (1.6)	0.0
Acneiform dermatitis	9 (1.4)	0.0
Skin irritation	7 (1.1)	0.0
Application site pain	5 (0.8)	0.0
Application site hemorrhage	4 (0.6)	1 (0.2)

Table 2 continued

	Adverse events, *N* (%)[a]	Serious adverse events, *N* (%)
Contact dermatitis	4 (0.6)	0.0
Pruritus	4 (0.6)	0.0
Application site pruritus	3 (0.5)	0.0
Dermatitis	3 (0.5)	0.0
Stomatitis	3 (0.5)	0.0
Eczema	2 (0.3)	0.0
Pain of skin	2 (0.3)	0.0
Eczema asteatotic	2 (0.3)	0.0
Photosensitivity reaction	2 (0.3)	0.0
Application site dryness	2 (0.3)	0.0
Application site erosion	2 (0.3)	0.0
Application site acne	1 (0.2)	0.0
Application site warmth	1 (0.2)	0.0
Anticonvulsant drug level increased	1 (0.2)	0.0
Agitation	1 (0.2)	0.0
Asteatosis	1 (0.2)	0.0
Application site swelling	1 (0.2)	0.0
Condition aggravated	1 (0.2)	0.0
Dermatitis bullous	1 (0.2)	0.0
Drug interaction	1 (0.2)	0.0
Dizziness	1 (0.2)	0.0
Erythema	1 (0.2)	0.0
Effusion	1 (0.2)	0.0
Eyelid erythema	1 (0.2)	0.0
Eyelid swelling	1 (0.2)	0.0
Flushing	1 (0.2)	0.0
Impetigo	1 (0.2)	0.0
Insomnia	1 (0.2)	0.0
Mood altered	1 (0.2)	0.0
Nasal discomfort	1 (0.2)	0.0
Paresthesia	1 (0.2)	0.0
Pain	1 (0.2)	0.0
Scab	1 (0.2)	0.0
Seborrheic dermatitis	1 (0.2)	0.0
Solar dermatitis	1 (0.2)	0.0
Skin hemorrhage	1 (0.2)	0.0

AEs adverse events
[a]AEs with an incidence of at least 1% are shown

Adverse Events

The overall incidence of AEs and serious AEs (SAEs) was 24.6% and 2.4%, respectively. The AEs with an incidence of at least 1%, as determined by preferred term, were acne (4.7%), application site irritation (2.8%), dry skin (2.2%), application site erythema (1.6%), acneiform dermatitis (1.4%), and stomatitis (1.3%). AEs and SAEs by preferred term are listed in Table 2, and the complete list of AEs and SAEs is presented in Supplementary Material Table S1.

Overall, 117 patients (18.4%) experienced ADRs. The ADRs with an incidence of at least 1%, as determined by preferred term, include acne (3.9%), application site irritation (2.8%), dry skin (2.2%), application site erythema (1.6%), acneiform dermatitis (1.4%), and skin irritation (1.1%). More than half of these ADRs occurred for the first time by week 12, with 5.2% (*n* = 33), 6.1% (n = 39), 5.0% (*n* = 30), 2.7% (*n* = 14), and 1.2% (*n* = 6) occurring within 0–4, 4–12, 12–26, 26–38, and 38–52 weeks. One serious ADR resulting in drug discontinuation was reported in one patient (0.2%) with application site hemorrhage, who eventually recovered (Table 2).

Table 3 Demographics and baseline characteristics of the included patients affecting improvement rate and safety of topical sirolimus 0.2% gel at week 52

Background factors	*N*	Effectiveness evaluation			*N*	Safety evaluation		
		Improvement rate *n* (%)	*p* value			Adverse drug reactions *n* (%)	*p* value	
Number of patients included in the analysis	630	398 (63.2)			635	117 (18.4)		
Gender								
Male	292	188 (64.4)	χ^2	0.559	293	45 (15.4)	χ^2	0.065
Female	338	210 (62.1)			342	72 (21.1)		
Age								
< 15 years	200	140 (70.0)	CA	0.010	203	25 (12.3)	CA	0.011
≥ 15 to < 65 years	423	255 (60.3)			425	91 (21.4)		
≥ 65 years	7	3 (42.9)			7	1 (14.3)		
Inpatient/outpatient								
Inpatient	13	8 (61.5)	χ^2	0.902	13	2 (15.4)	χ^2	0.775
Outpatient	617	390 (63.2)			622	115 (18.5)		
Duration of illness*								
< 3 years	29	19 (65.5)	CA	0.162	29	3 (10.3)	CA	0.279
≥ 3 to < 5 years	18	12 (66.7)			18	4 (22.2)		
≥ 5 to < 10 years	57	42 (73.7)			58	9 (15.5)		
≥ 10 to < 20 years	75	42 (56.0)			75	15 (20.0)		
≥ 20 years	109	64 (58.7)			109	22 (20.2)		
Allergy history*								
No	460	292 (63.5)	χ^2	0.054	463	81 (17.5)	χ^2	0.253
Yes	69	52 (75.4)			69	16 (23.2)		
Medical history*								
No	448	297 (66.3)	χ^2	0.090	450	75 (16.7)	χ^2	0.066
Yes	106	61 (57.5)			107	26 (24.3)		
Complications								
No	90	58 (64.4)	χ^2	0.787	92	19 (20.7)	χ^2	0.557
Yes	540	340 (63.0)			542	98 (18.1)		
Prior treatment								
No	377	235 (62.3)	χ^2	0.593	381	61 (16.0)	χ^2	0.055
Yes	253	163 (64.4)			254	56 (22.0)		

Table 3 continued

Background factors	*N*	Effectiveness evaluation			*N*	Safety evaluation		
		Improvement rate *n* (%)	*p* value			Adverse drug reactions*n* (%)	*p* value	
Duration of use*								
< 30 days	18	2 (11.1)	CA	< 0.001	20	7 (35.0)	CA	< 0.001
≥ 30 to < 90 days	59	17 (28.8)			60	17 (28.3)		
≥ 90 to < 180 days	52	22 (42.3)			53	9 (17.0)		
≥ 180 to < 270 days	32	22 (68.8)			32	9 (28.1)		
≥ 270 to ≤ 364 days	455	326 (71.6)			456	67 (14.7)		
Total dose*								
< 20 g	220	129 (58.6)	CA	0.005	222	38 (17.1)	CA	0.922
≥ 20 to < 60 g	257	157 (61.1)			259	51 (19.7)		
≥ 60 to < 120 g	73	54 (74.0)			73	12 (16.4)		
≥ 120 to < 180 g	47	34 (72.3)			47	10 (21.3)		
≥ 180 to < 240 g	19	14 (73.7)			19	3 (15.8)		
≥ 240 g	13	10 (76.9)			13	2 (15.4)		
Concomitant drugs*								
No	127	88 (69.3)	χ^2	0.115	139**	20 (14.4)	χ^2	0.177
Yes	502	310 (61.8)			495**	96 (19.4)		
Concomitant use of systemic mTOR inhibitors*								
No	515	324 (62.9)	χ^2	0.689	520**	90 (17.3)	χ^2	0.169
Yes	114	74 (64.9)			114**	26 (22.8)		

CA Cochran–Armitage trend test, *mTOR* mechanistic target of rapamycin
*Remaining was either absent or unknown/described
**Concomitant use before any adverse drug reactions occurred

Adverse Events of Special Interest

The incidence of photosensitivity as an ADR of topical sirolimus 0.2% gel treatment was 0.47% (3/635). Photosensitivity reaction was observed 162 and 74 days after treatment initiation in two female patients aged 13 and 24 years, respectively; solar dermatitis was observed 16 days after treatment initiation in a male patient aged 16 years. Although these AEs were mild and all three patients recovered, the possibility of a causal relationship between these AEs and topical sirolimus 0.2% gel cannot be ruled out.

Factors Affecting the Effectiveness and Safety of Topical Sirolimus 0.2% Gel

The association of demographics and baseline characteristics of the patients with the improvement rate of cutaneous manifestations or safety of topical sirolimus 0.2% gel use is

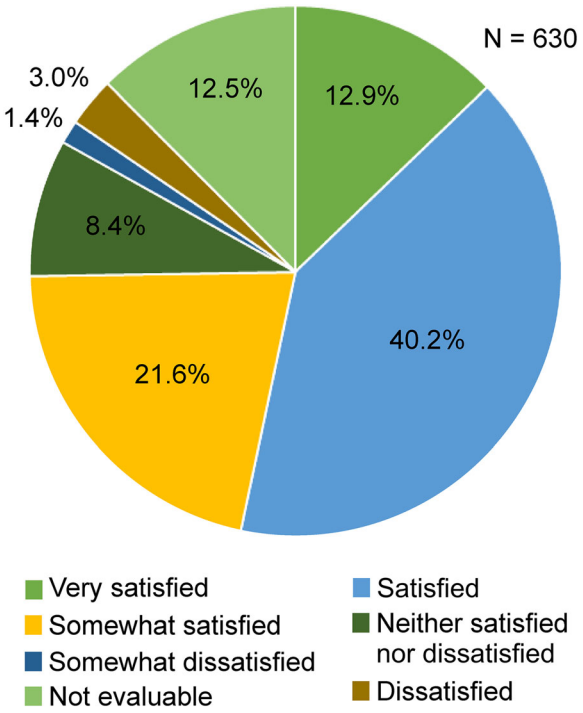


Fig. 3 Percentage distribution of patients based on the satisfaction level with their skin condition following topical sirolimus 0.2% gel treatment for TSC-related cutaneous manifestations

presented in Table 3. Among demographics and baseline characteristics, age, duration of use, and total dosage showed significant association with the overall improvement rate of cutaneous manifestations with topical sirolimus 0.2% gel use. A trend of higher improvement rate with lower age was observed for cutaneous manifestations with significant differences observed among the age groups (< 15, ≥ 15 to < 65, and ≥ 65 years, $p = 0.010$). Further subgrouping the patients aged ≥ 15 to < 65 years into 10-year intervals revealed a similar trend that the younger the age, the higher the improvement rate ($p = 0.042$, Supplementary Material Table S2). There was a significant trend that the longer the duration of drug use, the higher the improvement rate relative to 11% with < 30 days of use ($p < 0.001$). Similarly, there was a significant trend that the higher the total dose, the higher the improvement rate, relative to 58.6% with a total dose < 20 g ($p = 0.005$).

The incidence of ADRs was lower in the younger age group with a significant difference observed among the age groups (< 15, ≥ 15 to < 65, and ≥ 65 years, $p = 0.011$). However, the incidence rate of ADRs was similar among the age groups with no significant difference ($p = 0.477$) observed when the ≥ 15 to < 65-year age group was subdivided into 10-year intervals (Supplementary Material Table S2). We observed statistically significant ($p = 0.021$) differences in the ADR incidence rate in pediatric subgroups, with the 12- to 15-year age group showing the highest ADR incidence (22.0%), followed by the 3- to 6-year age group (12.1%), the 6- to 12-year age group (8.3%), and the < 3-year age group (0%). There was a significant trend that the longer the duration of use, the lower the ADR incidence, relative to a 35% incidence rate with < 30 days of use ($p = 0.001$).

The effectiveness and safety of the topical sirolimus 0.2% gel did not significantly differ between patients who received and did not receive oral mTOR inhibitors (64.9% vs. 62.9%, $p = 0.689$ and 22.8% vs. 17.3, $p = 0.169$, respectively). The improvement rate and safety of topical 0.2% sirolimus gel did not differ significantly between patients with renal impairment and those without (56.3% vs. 64.2%, $p = 0.169$ and 16.3% vs. 18.8%, $p = 0.587$, respectively), or between patients with hepatic impairment and those without (52.9% vs. 63.5%, $p = 0.375$ and 23.5% vs. 18.3%, $p = 0.585$, respectively).

Patient Satisfaction Level

The majority of patients were satisfied with the treatment. Overall, the patient satisfaction rate was found to be 53.0% when "very satisfied" and "satisfied" were evaluated as satisfied with their skin condition (Fig. 3).

DISCUSSION

We present the findings of 52-week PMS in Japan on the effectiveness and safety of topical sirolimus 0.2% gel treatment for TSC-related cutaneous manifestations. The majority of patients (74.8%) showed improvement in the

overall TSC-related cutaneous lesions at 52 weeks of treatment with topical sirolimus 0.2% gel, with facial angiofibroma showing the highest responder rate (86.2%). During the 52-week AE review period, 18.4% of patients experienced ADRs with topical sirolimus 0.2% gel. Efficacy was associated with age, duration of use, and total dosage. Safety was associated with age and duration of use. To the best of our knowledge, this is the first real-world evidence of topical sirolimus 0.2% gel and first to investigate the factors influencing the effectiveness and safety of topical sirolimus 0.2% gel in patients with TSC-related cutaneous manifestations. More than half of the patients (53.0%) were very satisfied or satisfied with topical sirolimus 0.2% gel treatment.

The clinical evidence for the effectiveness and safety of topical sirolimus 0.2% gel was established in previous studies [6–8]. Wataya-Kaneda et al. reported topical sirolimus 0.2% gel as an optimal concentration for the management of facial angiofibroma on the basis of a 12-week double-blind, placebo-controlled, dose-finding, phase II clinical trial which evaluated the improvement factor as measured by tumor size reduction and a lessening of the redness of the three target tumors [8]. The efficacy and safety of sirolimus 0.2% gel were further confirmed in a 12-week, placebo-controlled phase III clinical trial (n = 62; 27 pediatric and 35 adult patients) in Japan. After 12 weeks of treatment, 17% were rated as "markedly improved" and 43% as "improved" on the basis of composite improvement in the facial angiofibroma size and color, whereas none of the patients in the placebo group (n = 32) were rated "improved" [7]. Similarly, the response rates of cephalic plaques in the sirolimus group at week 8 (31%) and 12 (46%) were significantly higher (all p = 0 0.03) than those in the placebo group (0% and 6%, respectively) [7]. The 52-week long-term extension study revealed a rapid improvement rate in the facial angiofibroma during the first 12 weeks of treatment and gradually increased thereafter, reaching 78.2% at week 52. The rate of improvement in cephalic plaques increased over time, reaching 66.7% at 52 weeks. At week 52 of treatment, the improvement rate for hypomelanotic macules was 72.2%. Overall, 89.8% of patients rated their level of satisfaction as "very satisfied" or "satisfied" at 52 weeks of treatment [6]. Initial rapid improvement observed with topical sirolimus 0.2% gel may reach a plateau with no further dramatic improvement in the skin condition over time [9]. However, treatment continuation may be required for the maintenance of skin condition and to avoid recurrence. In a study by Wataya-Kaneda et al. [8], treatment discontinuation after 12 weeks of treatment with topical sirolimus 0.2% gel resulted in decreased response rates at week 4 of follow-up of treatment withdrawal, reflecting the transient mTOR inhibition by topical sirolimus. In a study conducted in the USA, the efficacy and safety of compounded topical sirolimus in patients over the age of 13 years showed improvement in 73% of patients with facial angiofibroma compared with 38% of patients treated with placebo [10]. The effectiveness of topical sirolimus was further established in a number of clinical trials and meta-analyses [9, 11–13].

Wataya-Kaneda et al. reported long-term safety of topical sirolimus 0.2% gel for the treatment of cutaneous manifestations in Japan, with discontinuations due to AEs (primary endpoint) observed only in two (2.1%) patients, eye irritation and erythema for one patient and contact dermatitis for another. Both AEs were mild, occurred within 1 week of treatment, and resolved without the need for clinical intervention [6]. In this real-world setting, 21.8% of patients discontinued the drug because of AEs. However, serious ADR resulting in drug discontinuation was reported in one patient with application site hemorrhage, who eventually recovered.

In a 12-week phase III study, the most common drug-related AEs for topical sirolimus 0.2% gel were application site irritation (37%), dry skin (37%), and acne (7%) [8]. Similarly, in the 52-week long-term extension study, the major drug-related AEs observed were application site irritation (30.9%), dry skin (27.7%), acne (20.2%), eye irritation (8.5%), pruritus (8.5%), erythema (7.4%), acneiform dermatitis (6.4%), and contact dermatitis (5.3%). The incidences of all these drug-related AEs were reduced to

half or less at week 68 after onset, and none of them were severe, and the majority subsided quickly [6]. In this real-world setting, the incidence of AEs was low, and included dry skin, application site irritation, acne, pruritus, and acneiform dermatitis. The eye irritation observed in clinical study was not observed in this real-world setting.

Previous clinical studies with the topical sirolimus 0.2% gel formulation revealed higher efficacy in children compared with adults [8, 9, 14], similar to that observed in this real-world evidence. In children, facial angiofibroma and cephalic plaques improved rapidly and showed significant differences at week 12 for facial angiofibroma. However, the final improvement rates at week 52 of treatment were comparable between adults and children [6]. The effectiveness of sirolimus gel over a short period of time in children may be attributed to an abundance of blood vessels and less thickened fibrous tissue compared to adults. In children with TSC, early intervention with topical sirolimus may help maintain the skin condition at near-normal levels [9, 11, 14]. However, concomitant use of oral mTOR inhibitors had no additive effect on the effectiveness of topical sirolimus gel in the current study. Similar findings were observed in a long-term study [6]. This could possibly be attributed to differences in sirolimus bioavailability in skin with different routes of administration.

Systemic mTOR inhibitor treatment for other TSC-related manifestations improved patients' skin conditions [15–19]. Concomitant use of mTOR inhibitors also showed no significant differences on the safety of topical sirolimus 0.2% gel treatment for cutaneous manifestations [20]. In this real-world setting, the safety of topical sirolimus 0.2% gel was comparable in patients who used and those who did not use mTOR inhibitors concurrently. Systemic exposure to mTOR inhibitors is associated with serious side effects, the majority of which are related to their immunosuppressive action [21]. Previous studies found that blood sirolimus levels were low, with a maximum concentration of 0.25 ng/mL after 12 weeks of treatment [8], and that most patients had a concentration of less than 1 ng/mL during 52 weeks of treatment [6].

The improvement rate of cutaneous manifestations with topical sirolimus 0.2% gel increased over time from 41.2% at week 4 to 74.8% at week 52. This could be due to the association between improvement rate and higher total dosage and longer duration. Okanishi et al. found similar results, reporting that patients treated for at least 24 months had a significant reduction in the size of facial angiofibromas [11]. Wataya-Kaneda et al. reported that treatment with topical sirolimus 0.2% gel over 52 weeks significantly improved facial angiofibroma, cephalic plaques, and hypomelanotic macules. It was reported that 89.8% of patients were "very satisfied" or "satisfied" with sirolimus 0.2% gel treatment [6]. A previous study found a significant correlation between the improvement factor and patient satisfaction with topical sirolimus (Spearman's correlation coefficient = − 0.477, $p = 0.003$) [8].

Early intervention with topical sirolimus gel appears to be effective and safe for the treatment of TSC-related cutaneous lesions, and it may keep the skin at near-normal levels in children and adults with TSC [10, 13, 14].

This study has some limitations. The major one is the lack of a control group, as this was a real-world PMS. Additionally, this is an interim analysis of a PMS that was conducted only in Japan; therefore, the findings should be interpreted accordingly with caution.

CONCLUSIONS

In this real-world setting, topical sirolimus 0.2% gel was found to be effective and generally well tolerated in the management of cutaneous manifestations, particularly facial angiofibroma, with greater than 80% responder rate by 12 weeks and 18.4% ADR incidence rate over 52 weeks in patients with TSC. The AEs with an incidence rate less than 5% include acne, application site irritation, dry skin, application site erythema, dermatitis, acneiform, and stomatitis. Among the patient demographics and baseline characteristics, age (< 15, ≥ 15 to < 65, and ≥ 65 years), duration of use, and total

dosage showed a significant association with the improvement rate. Safety was associated with age (< 15, ≥ 15 to < 65, and ≥ 65 years) and duration of use. Notably, a similar safety profile was observed when the broad age group (≥ 15 to < 65 years) was further categorized by 10-year intervals. More than half of the patients in this study were very satisfied or satisfied with the treatment.

ACKNOWLEDGEMENTS

The postmarketing data analyses was outsourced to CMIC Co., Ltd., Japan and the authors would like to thank them for their services. The authors express their sincere gratitude to Dr. Mari Wataya-Kaneda for providing critical review from a clinical perspective for this article developed based on the data analyses by CMIC Co., Ltd. We thank all physicians and investigators who cooperated in this surveillance and provided valuable data.

Funding. The PMS study was funded by Nobelpharma Co., Ltd., that also provided funding for the medical writing, editorial support, and Rapid Service fees.

Medical Writing/Editorial Assistance. The authors would also like to thank Bhavani K and SreeHarsha B, Enago Life Sciences, India, for their support in writing the manuscript and editing, which was funded by Nobelpharma.

Author Contributions. Akemi Egami, Shinji Takahashi, and Takeshi Kokubo provided substantial contributions to conception or design of the work, or the acquisition, analysis, or interpretation of data for the work; and drafting of the work or revising it critically for important intellectual content; Eric Beresford and Sreedevi Boggarapu provided scientific insights and interpretations of findings. Akemi Egami, Shinji Takahashi, and Takeshi Kokubo have full access to all of the study's data. All authors contributed to the manuscript's development and accept responsibility for the decision to submit this manuscript for publication.

Prior Presentation. Content within this article has been presented at the following meeting: 47th Society for Pediatric Dermatology Annual Meeting 07–10 July 2022 at Indianapolis, USA.

Disclosures. All authors are employees of Nobelpharma.

Compliance with Ethics Guidelines. This PMS was conducted as a part of the risk management plan of topical sirolimus 0.2% gel (Rapalimus®, Nobelpharma Co., Ltd., Tokyo, Japan), and in compliance with the Good Postmarketing Study Practice (GPSP) ordinance of the Ministry of Health, Labor and Welfare (MHLW). MHLW approval was subject to all patients using the medication being monitored. According to the MHLW's GPSP ordinance, the study's entire protocol does not need to receive approval from an ethical committee. Informed consent was not required under GPSP.

Data Availability. Akemi Egami, Shinji Takahashi, and Takeshi Kokubo have full access to all of the study's data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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