Dermatologic Manifestations of TSC and Management

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Disclosure:

Advisor and consultant for AFT Pharm, Abeona, Amryst, AUCTA, BridgeBio, Castle Creek, Eden Brand, KrystalBio, INC, Menlo Therapeutics, NobelPharm, LeoPharm, Novartis, Pfizer, Palvella Therapeutics, Regeneron.

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Objectives

1. Review cutaneous manifestations and diagnosis of TSC.
2. Review surveillance recommendations
3. Update on management of cutaneous manifestations.

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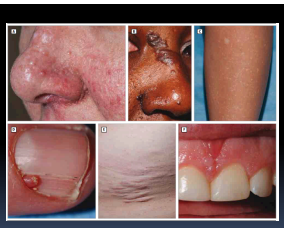
Consensus Statement

Dermatologic and Dental Aspects of the 2012 International Tuberous Sclerosis Complex Consensus Statements

Joyce M. C. Teng, MD, PhD; Edward W. Cowen, MD, MHSc; Mari Wataya-Kaneda, MD, PhD; Elizabeth S. Gosnell, DMD; Patricia M. Witman, MD; Adelaide A. Hebert, MD; Greg Mlynarczyk, DDS; Keyoumars Soltani, MD; Thomas N. Darling, MD, PhD



Common; Nonmalignant

JAMA Dermatology July 16, 2014

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Table 1. Revised Diagnostic Criteria for Tuberous Sclerosis Complex[a]

1998	2012
Genetic Criterion	
None	Pathogenic mutation in *TSC1* or *TSC2*
Major Features	
Facial angiofibromas or forehead plaque	Angiofibromas (≥3) or fibrous cephalic plaque
Hypomelanotic macules (≥3)	Hypomelanotic macules (≥3, at least 5 mm in diameter)
Nontraumatic ungual or periungual fibroma	Ungual fibromas (≥2)
Shagreen patch (connective tissue nevus)	Shagreen patch
Multiple retinal hamartomas	Multiple retinal hamartomas
Cortical tuber	Cortical dysplasias
Subependymal nodule	Subependymal nodules
Subependymal giant cell astrocytoma	Subependymal giant cell astrocytoma
Cardiac rhabdomyoma, single or multiple	Cardiac rhabdomyoma
Lymphangioleiomyomatosis	Lymphangioleiomyomatosis[b]
Renal angiomyolipoma	Angiomyolipomas (≥2)[b]
Minor Features	
Multiple randomly distributed pits in dental enamel	Dental enamel pits (≥3)
Gingival fibromas	Intraoral fibromas (≥2)
"Confetti" skin lesions	"Confetti" skin lesions
Nonrenal hamartomas	Nonrenal hamartomas
Multiple renal cysts	Multiple renal cysts
Retinal achromic patch	Retinal achromic patch
Hamartomatous rectal polyps	
Bone cysts	
Cerebral white matter migration lines	

- Skin and dental findings comprise 4/11 major features;
- 3/6 minor features in the diagnostic criteria.

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Diagnosis of TSC

- A definite diagnosis =
  - 2 major features
  - 1 major and 2 or more minor features
- a pathological mutation in TSC1 or TSC2 is diagnostic

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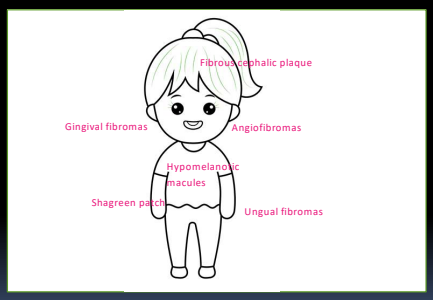
Skin Manifestations in TSC



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Current Recommendations

- An initial comprehensive dermatologic exam should be performed by a dermatologist who is experienced in the recognition of TSC-related skin lesions.
- Subsequent skin exam should be performed annually or every 3 to 6 months, with focus on rapidly changing or symptomatic lesions
- Consider biopsy when appropriate.

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Surveillance (Cont')

- Intervention may be indicated for TSC skin or oral lesions that are bleeding, symptomatic, disfiguring, or negatively affecting function.

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Management of Dermatologic Manifestations in TSC

- Hypomelanotic macules (no Tx needed)
- Shagreen patches (no Tx needed)
- Ungual fibromas (excision or ablative laser)
- Cephalic plaques (Laser; excision, removed by staged excision, or no treatment)
- Facial angiofibromas (vascular or/and ablative laser; dermabrasion; shave removal; electro-desiccation; PDT)

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Surgical Considerations & Risks

- Clinical responses are transient;
- Rapid recurrence
- Surgical complications (pain, bleeding, infection, scar etc.)
- Post Op recovery depending on the complexity of the procedure
- General anesthesia
- $$$

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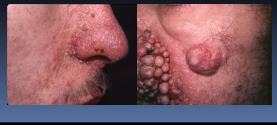
Facial Angiofibroma: A therapeutic challenge in TS

- Occur in 70-80% of TS patients
- Progressively enlarge and multiply with time
- Highly visible markers of disease which may spontaneously bleed, impair vision, and cause emotional distress .
- Most of therapies were not effective in preventing early lesions, therefore have less satisfactory.



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To Treat or Not to Treat

- Age
- Severity
- Symptoms: i.e. bleeding
- Comorbid medical risks

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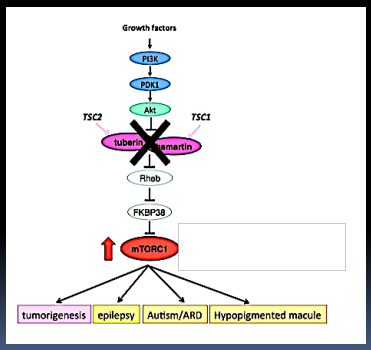

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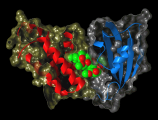
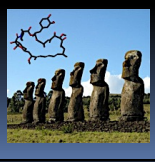
Sirolimus



- An **immunosuppressant** used in transplant patients since 1980s'.
- **Anti-tumorgenesis effects**, exerted through
- **Anti-angiogenic effects**



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Q1. How well does it work?

Q2. How Safe is the treatment?

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Balestri et al. JEADV 29 14-20 2015

- 94% response rate in the initial **16** reports
- **Concentration used:** 0.003 to 0.1%
- **Frequency of use:** 1-2 x daily
- **Vehicle used:** ointment, cream, gel, solution
- **AE**: 4/84 pt (irritation, HA, perioral dermatitis)
- **Monitoring:** no detectable sirolimus in serum among most of the patients

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W-Kaneda et al. JAMA Dermatol. 2017;153(1):39-48.

JAMA Dermatology | Original Investigation

Efficacy and Safety of Topical Sirolimus Therapy for Facial Angiofibromas in the Tuberous Sclerosis Complex
A Randomized Clinical Trial

Mari Wataya-Kaneda, MD, PhD; Ayumi Nakamura, BPharm; Mari Tanaka, MD, PhD; Misa Hayashi, MD; Shoji Matsumoto, PhD; Koji Yamamoto, PhD; Ichiro Katayama, MD, PhD

- Tx: Sirolimus gel 2x daily
- A double-blind, placebo-controlled, parallel-group, dose-escalation, phase 2
- 18 aged 3 to 18 years; 18 aged 19 to 65 years
- 3 groups (n = 12 each)
- Randomized to receive sirolimus gel concentrations of 0.05%, 0.1%, or 0.2%or placebo using a web-response system in a 2:1 fashion.

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- **Results:**
  - 0.2 % is effective for both children and adults
  - 0.1%, 0.05% are only effective for children
- **AE:**
  - Dryness (13 patients [36%])
  - Irritation (11 patients [31%]).
- **Laboratory Monitoring:**
  - Low blood levels (<0.25 ng/mL) detected in 1 adults [25%] in the 0.1% adult group; and 2 [50%] in the 0.2% adult subgroup)
  - 1 children [25%] in the 0.05% child subgroup, 2 patients [50%] in the 0.1% child subgroup; and 4 patients [100%] in the 0.2%child subgroup).

W-Kaneda et al. JAMA Dermatol. 2017;153(1):39-48.

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May 2018

JAMA Dermatology | Original Investigation

Efficacy and Safety of Topical Rapamycin in Patients With Facial Angiofibromas Secondary to Tuberous Sclerosis Complex
The TREATMENT Randomized Clinical Trial

Mary Kay Koenig, MD; Cynthia S. Bell, MS; Adelaida A. Hebert, MD; Joan Roberson, RN, BSN; Joshua A. Samuels, MD, MPH; John M. Slopis, MD; Patti Tate, RCP, CCRP; Hope Northrup, MD; for the TREATMENT Trial Collaborators

- 179 patients randomized
  - 59 in the 1% sirolimus group,
  - 63 in the 0.1% sirolimus group,
  - 57 in the vehicle-only group).
- The mean age was 20.5 years (range 3-61 years)

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2018 JAMA Derm Koenig et al.

- Clinically improvement observed in 1% and 0.1% group
- Most of the improvement realized within the **first month.**
- At 6 mo, AGS mean improvement for 1% rapamycin was 16.7 points compared with 11.0 for 0.1% rapamycin and 2.1 points for vehicle only ($P < .001$ for 1% and 0.1% vs vehicle only).
- Topical sirolimus well-tolerated, with no measurable systemic absorption.
- Nearly all AEs were mild, with no drug-related moderate, severe, or serious events.

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2018 JAMA Derm Koenig et al.

CONCLUSIONS

- Topical sirolimus appears effective and safe for treatment of TSC-related facial angiofibromas.
- Preferred dose was 1% once daily.

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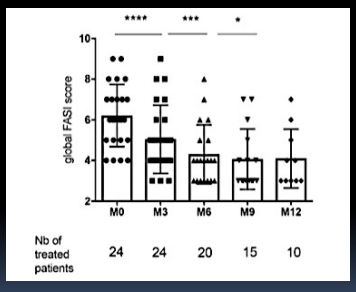
Q3. When does treatment plateau?



J Am Acad Dermatol. 2017 Sep;77(3):464-472. Malissen et al.

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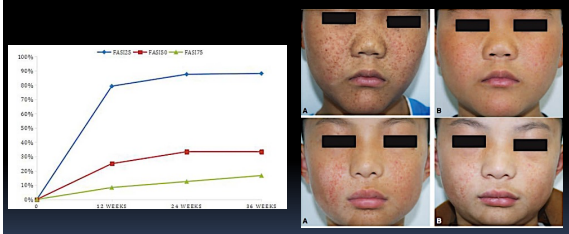

Pediatric Dermatology Vol. 34 No. 5 572–577, 2017

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Q4. Frequency of Treatment to Maintain

- Tx: topical 1% sirolimus once daily → 3x/wkly
- Twenty-five patients 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.**
- Treatment was well tolerated with no serious adverse events

J Am Acad Dermatol. 2017 Sep;77(3):464-472. Malissen et al.

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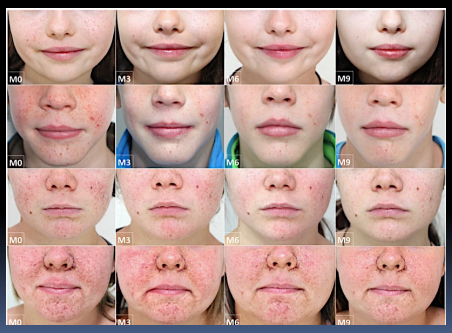
Q5. Benefit of Early Treatment?



J Am Accad Dermatol. 2017 Sep;77(3):464-472. Malissen et al.

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Q6. Does It Work In Combination With Laser?

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Lasers Surg Med. **2010** Jul;42(5):357-60. **New technique using combined pulsed dye laser and fractional resurfacing for treating facial angiofibromas in tuberous sclerosis. Weiss et al.**

Targeted topical and combination **laser** surgery for the treatment of **angiofibromas**. Bae-Harboe YS, Geronemus RG. **Lasers** Surg Med. **2013** Nov;45(9):555-7.

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Q7. Does it work for other TS lesions?

Tx: 0.1% sirolimus ointment x 36 weeks
Patients: 29 children

Results:
- Facial AF: CC (17%)
- 27/29 (93%) hypomelanotic macules improved

Pediatric Dermatology Vol. 34 No. 5 572–577, 2017

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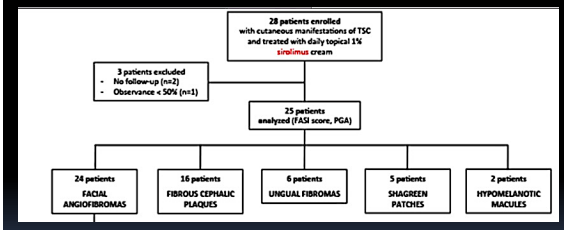
Treating all TSC lesions (Cont)



J Am Acad Dermatol. 2017 Sep;77(3):464-472. Malissen et al.

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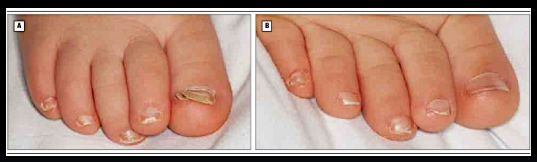
Sirolimus for Ungual Fibroma



Sol (1 mg/ml)

JAMA Derm 150: 9 sept 2014.

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Topical Sirolimus for Cephalic Plaque

JAMA Dermatol. 2017 Jan 1;153(1):39-48.

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Q8. Any Possible Adverse Effects?

- Irritation
- Acne
- Photosensitivity

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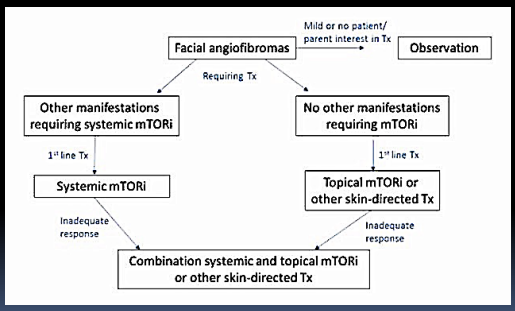
Q9. When to consider systemic therapy?



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Q10. Additional Management Rec?

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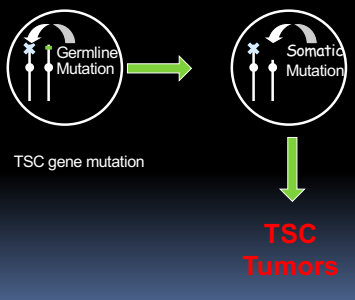
Tumorigenesis



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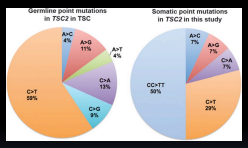
Hum Mol Genet. 2014;23:2023-9. **Sun exposure causes somatic second-hit mutations and angiofibroma development in tuberous sclerosis complex**



UV Signature
Somatic Mutations

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Tumorigenesis

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Sun Protective Measures

- Avoid mid day sun exposure
- Wear protective clothing
- Wide-brimmed hat
- Wrap around sun glasses

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Broad Spectrum Sunscreen

- UVA & UVB protection
  - benzophenones (oxybenzone)
  - avobenzone (Parsol 1789)
  - ecamsule (Mexoryl SX)
  - sulisobenzone
  - titanium dioxide
  - zinc oxide

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AAD Guidelines

https://www.aad.org/sun-protection/sunscreen-faqs

- **Broad-spectrum (UVA/UVB protection)**
- **SPF 30 or higher**
- **Water resistance**
- **Barriers**
  - Cost
  - Cosmetic elegance
  - Effectiveness

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SPF 100+ sunscreen is more protective against sunburn than SPF 50+ in actual use: Results of a randomized, double-blind, split-face, natural sunlight exposure clinical trial

199 participants in Colorado.

After 6.1 ± 1.3 hours of sun exposure, 110 participants (55.3%) were sunburned on their SPF 50 side, and 10 (5%) were sunburned on the SPF 100 side.

40.7% of the participants (81 of 199) exhibited **increased erythema** scores (by ≥1) on the SPF 50+ protected side as compared with **13.6%** (27 of 199) on the SPF 100+ protected side.

Williams et al. JAAD Vol 78, (5), May 2018, P 902-910.e2

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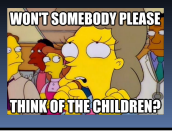
Sunscreen and Children

- Childhood sun exposure
  - Increased risk in adulthood
- Same guidelines
- **Physical sunscreen** in children 6 mo to 2 yo
  - Safety concern
    - High body surface to body mass ratio
    - Immature skin with increased absorption
    - Metabolism and excretion



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Safety of Sunscreen (Cont.)

- **Vitamin D**
  - Maintain adequate levels via diet & supplementation **(85%)**

Life Stage Group (age and gender)	Calcium RDA (mg/d)[a]	Calcium Upper Limit (UL) (mg/d)	Vitamin D RDA (IU/d)[a]	Vitamin D Upper Limit (UL) (IU/d)
0-6 mo (M+F)	200[b]	1000[b]	400[b]	1000[b]
6-12 mo (M+F)	260[b]	1500[b]	400[b]	1500[b]
1-3yr (M+F)	700	2500	600	2500
4-8yr (M+F)	1000	2500	600	3000
9-13yr (M+F)	1300	3000	600	4000
14-18yr (M+F)[c]	1300	3000	600	4000
19-30yr (M+F)[c]	1000	2500	600	4000
31-50 yr (M+F)	1000	2500	600	4000
51-70 yr (M)	1000	2000	600	4000
51-70yr (F)	1200	2000	600	4000
71+yr (M+F)	1200	2000	800	4000

Wang, SQ, Burnett, M, Lim, HW. Arch Dermatol, 2011; 147:865)

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Summary

- Topical sirolimus could be a safe and effective treatment for facial angiofibromas.
- The treatment is effective for other TSC-associated cutaneous manifestations.
- Long term maintenance treatment is needed to prevent recurrence.

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Summary II

- Early intervention is indicated for bleeding, symptomatic, or potentially disfiguring TSC skin lesions.
- Choice of treatment is case dependent.
  - Surgical approaches may be preferable to topical sirolimus for thick lesions that may not be less responsive to topical therapy

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Take Home Messages

- Comprehensive dermatologic evaluation and management is essential for the care of pediatric and adult TSC patients
- Anticipatory guidance regarding expectations and potential treatments is advised
- Individuals affected by TSC should practice good sun protection.

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