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TSC Alliance Webinar: What's Facial
Angiofibroma Associated With TSC and How Can
It Be Managed

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Conflicts of Interest

- Nobelpharma America, LLC is sponsoring this event and has provided financial support for the speakers to participate
- Employees of Nobelpharma are attending and participating in this event
- Dr. Joyce Teng is a consultant for Nobelpharma America and a scientific advisor for the TSC Alliance

Today's Agenda

- Welcome & Introductions – Eric Beresford, VP, Head of Medical Affairs at Nobelpharma America
- What Is Facial Angiofibroma Associated with TSC
- Social and Psychological Impact of Facial Angiofibroma
- Take Care of Your Skin
- What to Know About Treatments
- Q&A



What Is Facial Angiofibroma
Associated with TSC

Social and Psychological Impact of
Facial Angiofibroma

Take Care of Your Skin

What to Know About Treatments

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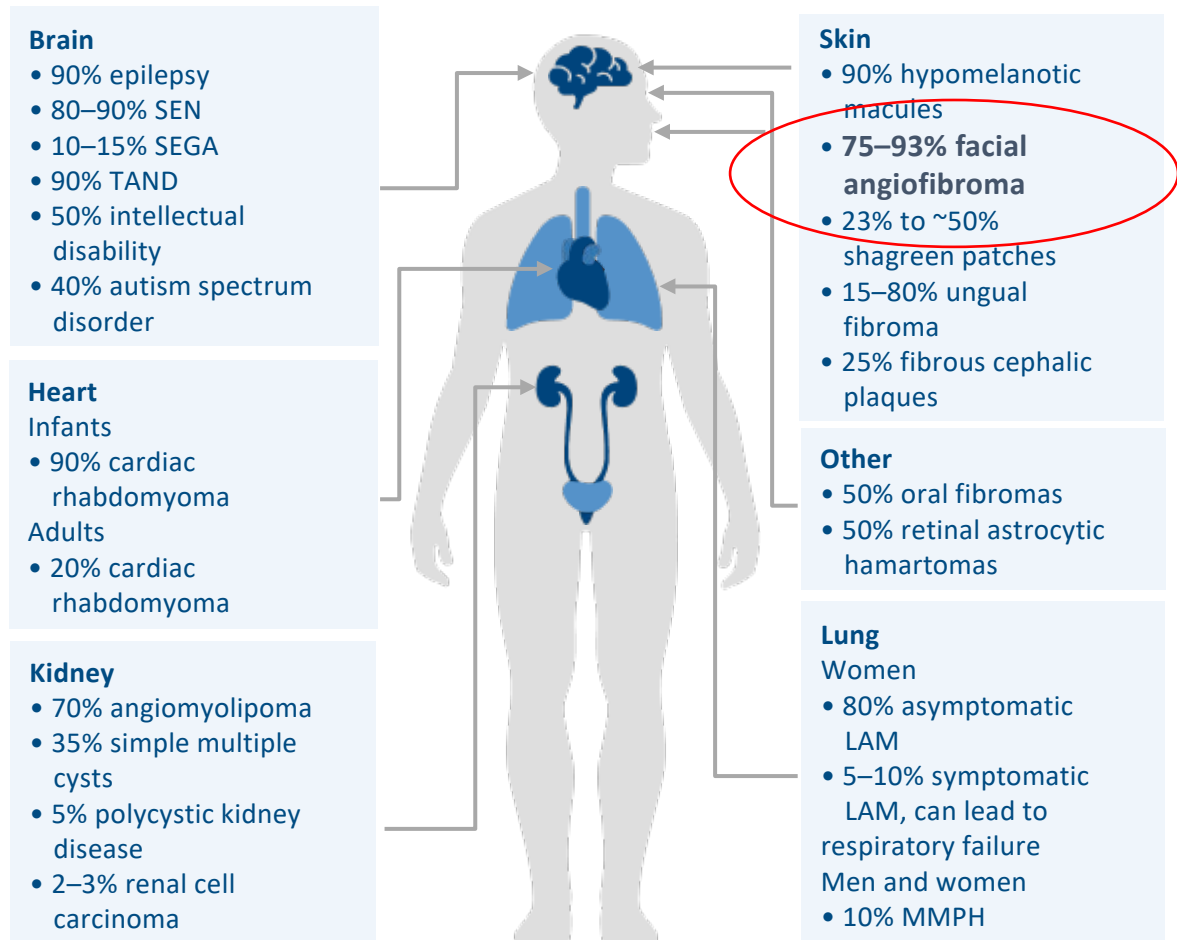
What is Facial Angiofibroma Associated with TSC

TSC Can Affect Any Organ System



TSC affects **~50,000** people in the **US**¹⁻⁴:

- Occurs in **all races** and ethnicities
- **No variation** based on **sex**
- Usually **diagnosed in children and infants** (>50% of patients diagnosed **by age 17 years**)



Adapted from Henske EP et al. 2016¹

1. Henske EP, et al. Nat Rev Dis Primers. 2016;2:16035.

1. Henske EP, et al. Nat Rev Dis Primers. 2016;2:16035; 2. Tuberous Sclerosis Alliance. A Report from the Tuberous Sclerosis Alliance's Externally-Led Patient-Focused Drug Development Meeting 2017. Available from: www.tsalliance.org/wp-content/uploads/2018/01/Voice-of-the-Patient-Tuberous-Sclerosis-Alliance.pdf. Last accessed August 2020; 3. Beresford E, et al. Facial angiofibroma related to tuberous sclerosis complex and the use of topical rapamycin in the United States: a survey of caregivers and individuals with TSC. Poster presented at the 45th annual meeting of the Society for Pediatric Dermatology (SPD 2020), July 10-12, 2020; 4. Micozkadioglu H, et al. Ren Fail. 2010;32(10):1233-1236;

Major and Minor Diagnostic Criteria

Major Criteria	Minor Criteria
Hypomelanotic macules (≥ 3 ; at least 5 mm diameter)	“Confetti” skin lesions
Angiofibroma (≥ 3) or fibrous cephalic plaque	Dental enamel pits (≥ 3)
Ungual fibromas (≥ 2)	Intraoral fibromas (≥ 2)
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Multiple cortical tubers and/or radial migration lines	Nonrenal hamartomas
Subependymal nodule (≥ 2)	Sclerotic bone lesions
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
LAM*	
Angiomyolipomas (≥ 2)*	

*A combination of the 2 major clinical features LAM and angiomyolipomas without other features does not meet criteria for a definite diagnosis.

Northrup H, Koenig MK, Pearson DA, Au KS. Tuberous sclerosis complex. July 13, 1999. Updated April 16, 2020. Accessed April 21, 2021. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews. University of Washington, Seattle; 1993-2021.

Facial Angiofibroma Is One of the Most Common Skin Conditions Associated With TSC

- Skin conditions appear in almost all (>90%) people with TSC
- Facial angiofibromas are benign tumors found on between 75% to 93% of people with TSC
 - Typically present as pinkish or reddish bumps on nose and cheeks
 - Usually develop at ages 2-5 years
 - Present in ~80% of TSC patients by the time they reach adolescence
 - Proliferate and grow in size gradually (to ≥ 3 mm in diameter)
 - Vary in color depending on fibrous tissue and blood vessel density
 - Presence of ≥ 3 tumors is one of major TSC diagnostic features



Social and Psychological Impact of Facial Angiofibroma

Impact of Facial Angiofibroma



FACIAL ANGIOFIBROMAS ARE ASSOCIATED WITH PSYCHOLOGICAL AND SOCIAL BURDEN

- Facial angiofibromas can **bleed** easily, become infected, and **impair function**
- They may also cause **pain** and, if left untreated, may result in **disfigurement**, and increased **psychosocial distress**
- These tumors may also be a **psychological and social burden** for people living with this condition
- Patients have reported that facial angiofibroma can have **negative effects on appearance and self-image**, causing some people to avoid social situations

Significant Psychosocial Impacts of Acne Vulgaris



Work/social situations



Questions, concerns, and advice from others



Developmental delays



Fear of school



Bullying



Behavioral issues/adjustment disorders



Confidence



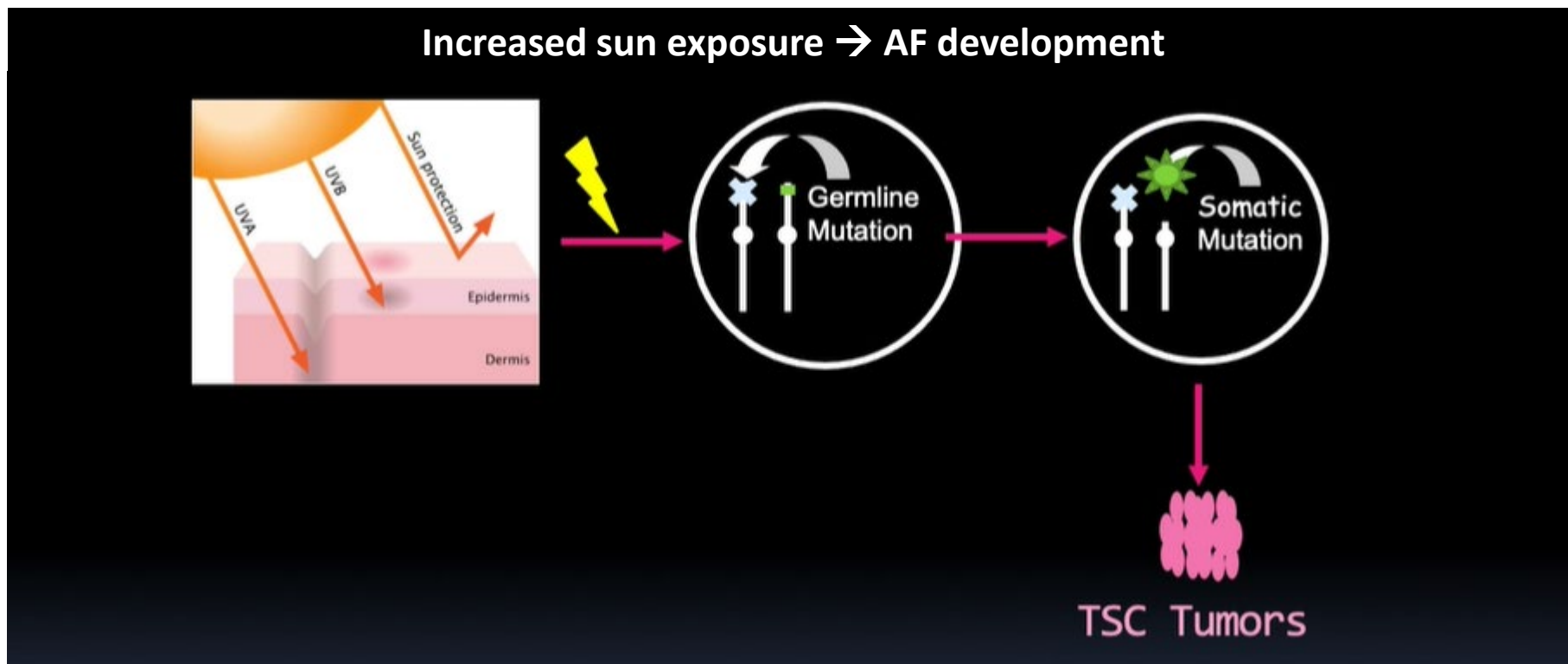
Appearance/self-image

In a study evaluating young adolescents with acne vulgaris

- Moderate/severe experienced greater psychosocial and emotional impairment
- Body image modified proportionally to the severity of acne
- Girls and boys are equally affected
- Impact is proportional to severity
- More severe disease associated with greater effect on QoL with implications for:
 - Self-esteem
 - Body image
 - Relationships with others

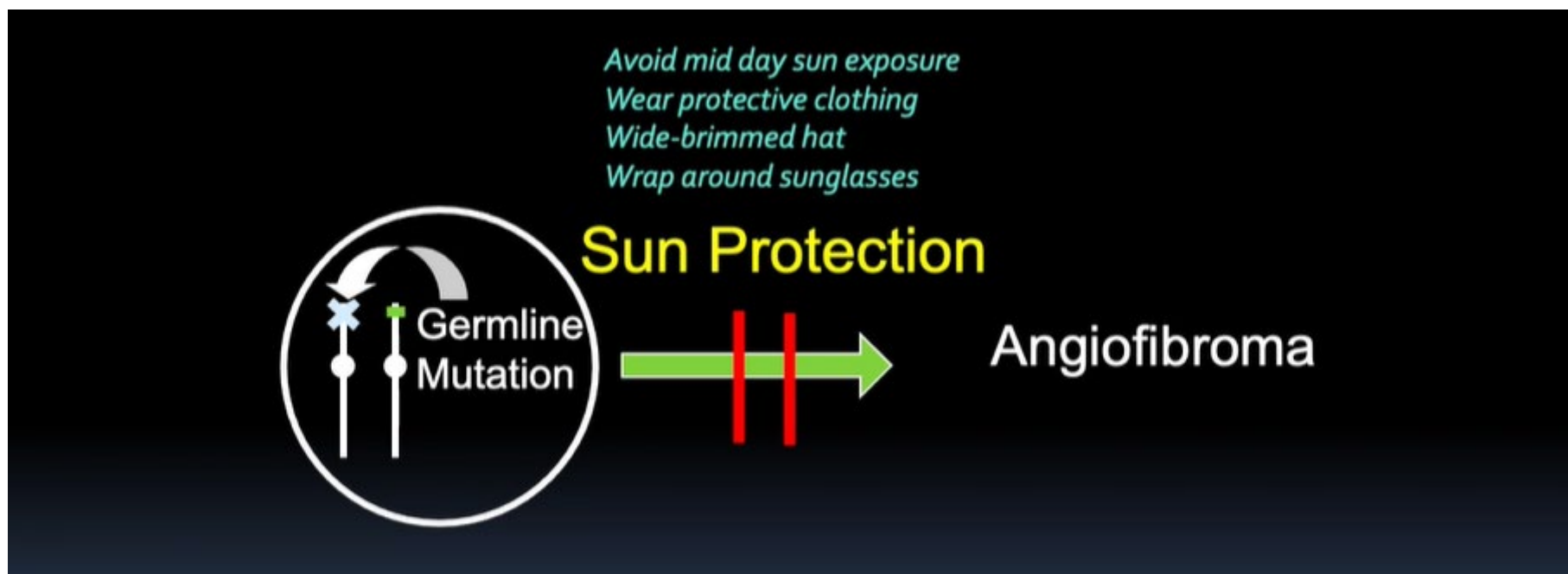
Care Prevention of Facial Angiofibroma

Sun Exposure May Have a Role in the Development of Facial Angiofibroma



Hum Mol Genet. 2014; 23:2023-9

Sun Protection Is Important To Help Prevent Angiofibroma



Hum Mol Genet. 2014; 23:2023-9



Follow Guidelines and Use Sunscreen To Protect Yourself

<https://www.aad.org/public/everyday-care/sun-protection>

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

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

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

Sun Protection Is Critical for Children As Well

- Physical sunscreen in children 6-months to 2-years old
 - Safety concern
 - High body surface to body mass ratio
 - Immature skin with increase absorption
 - Increased skin sensitivity
- Other physical protection
 - Hats
 - Sun protective clothing

Treatment Options for Facial Angiofibroma

Challenges in the Diagnosis and Treatment of Facial Angiofibroma

- Who diagnoses? Who prescribes?
 - Pediatricians/neurologists often may be the first to see patients with TSC, and they may see patients more frequently. Therefore, they often collaborate with dermatologists to manage patients' facial angiofibroma.
 - Dermatologists, especially pediatric dermatologists likely will be more up to date on potential treatment options and manage problematic or symptomatic facial angiofibromas.
 - **Facial angiofibroma can be misdiagnosed as acne in young children and adolescents.**

Treatment Considerations

- Age
- Severity
- Symptoms: i.e. bleeding
- Comorbid medical risks
- Newly suspected or diagnosed patients with TSC should be re-evaluated every six months

How well does it work?
How safe is the treatment?

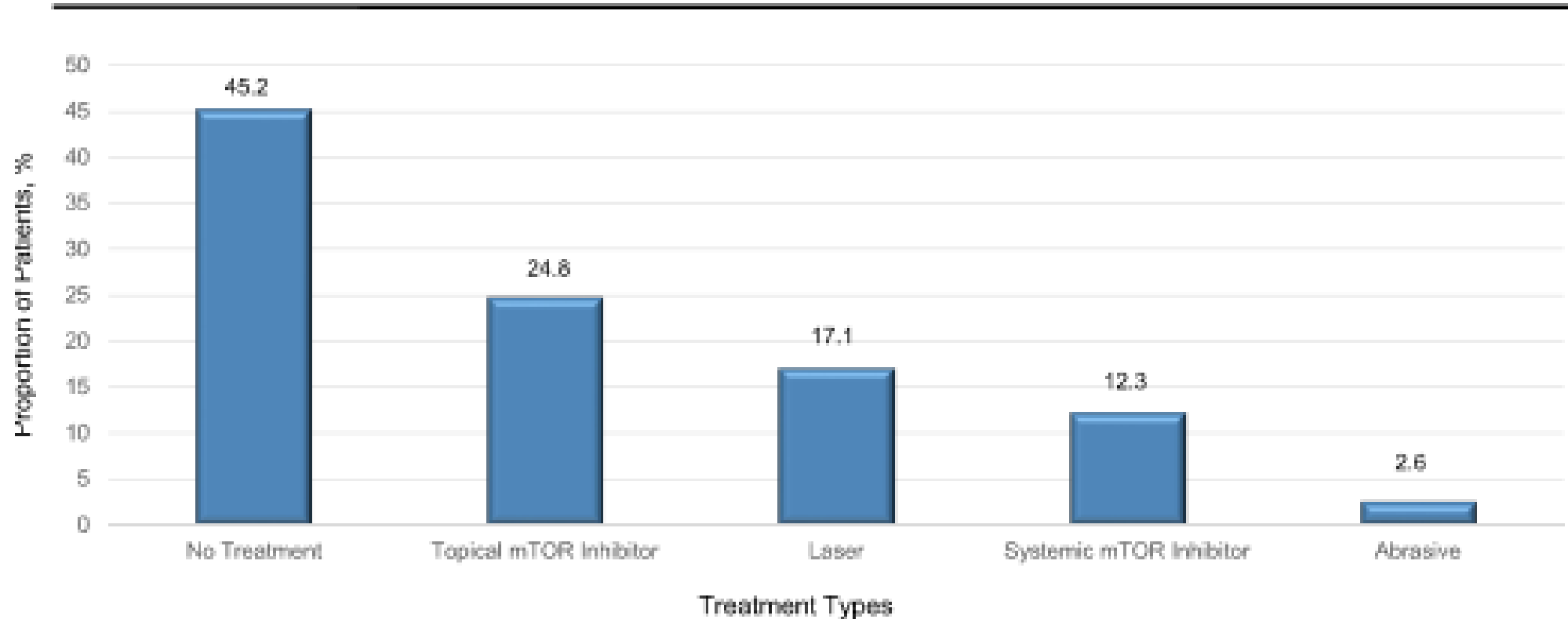
2021 International TSC Consensus Conference Recommendations on Clinical Surveillance and Management of TSC-Related Skin Manifestations

Newly suspected or diagnosed patients with TSC: All patients should undergo a detailed dermatologic and dental exam to be evaluated for facial angiofibromas, fibrous cephalic plaques, and hypomelanotic macules or confetti lesions

For already diagnosed patients with definite or possible TSC: Provide ongoing education on sun protection. Watch for improvement in skin lesions over several months. If lesions do not improve, or if earlier intervention is indicated, then consider use of surgical approaches. For protuberant lesions, consider surgical approaches (e.g., excision, lasers). Skin lesions that are smaller and flatter appear to respond better to topical sirolimus than bulky lesions, so early treatment is recommended. For flat or minimally elevated lesions, topical mTOR inhibitor treatment is recommended.

1. Northrup H, Aronow ME, Bebin EM, et al. *Pediatr Neurol.* 2021;123:50-66.

Treatment Received by People With Facial Angiofibroma



Source: TSC Alliance Natural History Database

Surgical Removal of Angiofibromas



PHYSICAL REMOVAL¹⁻³

- May include surgical removal, laser therapy, dermabrasion
- Can be invasive and painful; with the risk of scarring, dyspigmentation, and post-procedure infection
- Recurrence rates are $\leq 80\%$ and follow-up treatment is frequently required
- May require anesthesia, which may be associated with risks and complications, particularly in children
- Can be costly

FDA, Food and Drug Administration; mTOR, mammalian target of rapamycin; TSC, tuberous sclerosis complex.

1. Koenig MK, et al. JAMA Dermatol. 2018;154(7):773-780; 2. Macri A, Tanner LS. Cutaneous Angiofibroma. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2020, StatPearls Publishing LLC.; 2020; 3. Salido-Vallejo R, et al. Actas Dermosifiliogr. 2014;105(6):558-568;

Medications



MTOR INHIBITORS¹⁻⁶

- Both oral and topical formulations of mTOR inhibitors (e.g., sirolimus, everolimus) are used to treat TSC-related complications but may not be indicated for facial angiofibroma
- Oral mTOR inhibitors have been shown to improve facial angiofibroma but their use is generally restricted due to concerns around systemic side effects (e.g., stomatitis, mouth ulcers, marrow suppression, infections)
- International consensus recommendations suggest topical mTOR inhibitors be used for flat or minimally elevated angiofibromas¹.

FDA, Food and Drug Administration; mTOR, mammalian target of rapamycin; SEGA, subependymal giant cell astrocytoma; TSC, tuberous sclerosis complex.

1. Salido-Vallejo R, et al. *Actas Dermosifiliogr.* 2014;105(6):558-568; 2. Krueger DA, Northrup H. *Pediatr Neurol.* 2013;49(4):255-265; 3. Teng JM, et al. *JAMA Dermatol.* 2014;150(10):1095-1101; 4. Tuberous Sclerosis Alliance. A Report from the Tuberous Sclerosis Alliance's Externally-Led Patient-Focused Drug Development Meeting 2017. Available from: www.tsalliance.org/wp-content/uploads/2018/01/Voice-of-the-Patient-Tuberous-Sclerosis-Alliance.pdf. Last accessed August 2020; 5. Amin S, et al. *QJM.* 2019;112(3):171-182; 6. Crall C, et al. *Pediatr Dermatol.* 2016;33(5):518-525.

Possible Adverse Reactions From Topical mTOR Inhibitors

- Application site irritation / Acne / Rash
- Dry skin / Itching
- Photosensitivity
- Eye redness
- Skin bleeding / Skin irritation

Key Takeaways To Manage Facial Angiofibroma

- Baseline comprehensive exam
- Subsequent skin exam
 - Annually or every 3 to 6 months
- Consider biopsy when appropriate
- Early intervention
- Sun protection
- Choice of treatment varies among the patients.
 - Surgical approaches may be preferable for symptomatic large tumors
- Patient will benefit from collaborative multidisciplinary care



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Thank You