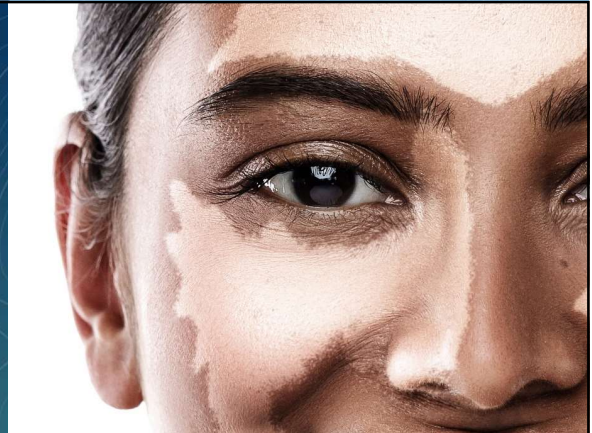


Navigating Novel Terrain in Vitiligo Management:



A Practical, Patient-Centric Review



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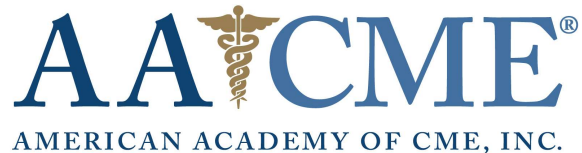


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Establishing Context

Vitiligo Presentation, Prevalence, and Patient Burden

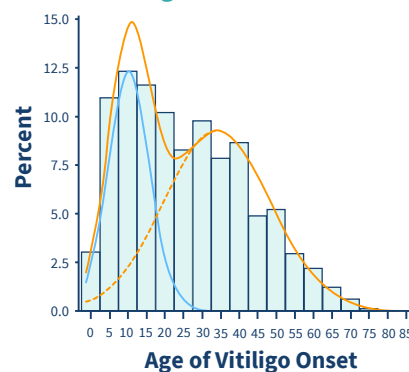
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Vitiligo

- 1% prevalence in US and Europe; up to 8.8% in India
- ½ of all patients have onset of disease prior to age 20
 - 70-80% before age 30
- Equal incidence in men and women but females experience peak in onset in first decade of life and for males it is in the fifth decade of life
- Unpredictable disease course
- Itch associated in up to 20% of patients
- Treatment has historically been difficult
- Spontaneous repigmentation is possible but uncommon (about 10% of patients)



Vitiligo Onset is Bimodal



AL-smadi K, et al. *Cosmetics*. 2023; Gandhi K, et al. *JAMA Dermatology*. 2022; <https://www.aad.org/public/diseases/a-z/vitiligo-causes>; Varma K, et al. *IP Indian J Clin Exp Dermatol*. 2022; Alikhan A, et al. *J Am Acad Dermatol*. 2011; Jin Y, et al. *Nat Commun*. 2019.

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Disease Presentation

- Well demarcated, patchy, depigmented macules and patches
- Accentuates with wood's lamp
- Signs of Disease Activity
 - **Confetti-like depigmentation:** 1-5 mm depigmented macules in clusters, often at edges of existing lesions
 - **Trichrome lesions:** Hypopigmented zone between normal and depigmented skin
 - **Koebner phenomenon**



Aboul-Fettouh N, et al. *J Am Acad Dermatol.* 2017.

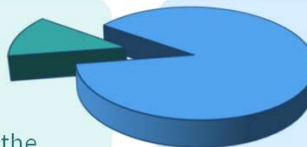
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Segmental vs Non-Segmental Vitiligo

Segmental 10-15%
of cases

- Predictable course
- Rapid spreading restricted to the segment that lasts up to 2 years and then stabilization
- Typically more difficult to treat
- Early intervention is important
- Surgical intervention can be used if it has been there a long time



Non-Segmental 85-90%
of cases

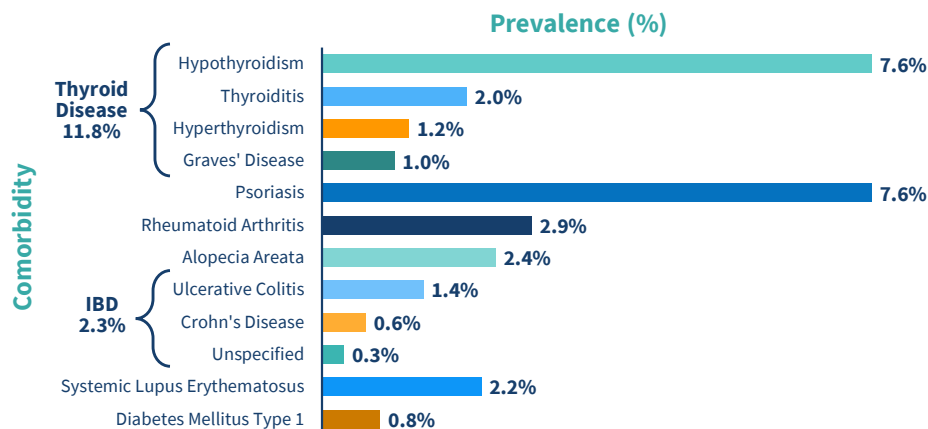
- Unpredictable course
- Periods of stability and periods of spreading
- Symmetric body distribution
- Distributions: Focal, Vitiligo Vulgaris (scattered), Acrofacial, Universal

Unclassified: Focal or mucosal (1 site in isolation)

Ezzedine K, et al. *Pigment Cell Melanoma Res.* 2012; Bergqvist C, et al. *Dermatology.* 2020; Ezzedine K, et al. *J Am Acad Dermatol.* 2023.

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Prevalence of Comorbidities in Vitiligo



Sheth VM, et al. *Dermatology*. 2013.

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“Because **skin color plays a major role in an individual’s perception of health, wealth, worth and desirability**, pigmentary disfigurements may influence social interactions. Vitiligo may even lead to social exclusion in certain societies.

Therefore, vitiligo is considered to be one of the **major medical disorders** ...vitiligo is **often considered as a harmless, cosmetic skin disorder**, whereby **the importance of treating patients with vitiligo is often underestimated.**”

Linthorst Homan MW, et al. *J Am Acad Dermatol*. 2009.

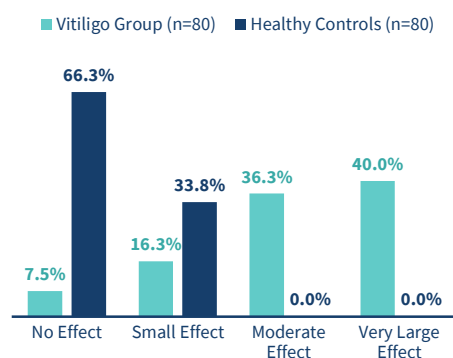
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Psychological Burden of Vitiligo

- In QOL studies, impact of vitiligo is similar to atopic dermatitis, psoriasis, and acne
- Patients can feel stressed and stigmatized by the depigmentation
- Major impact on self-esteem and confidence
- Given that **most patients have onset before age 20**, these patients are facing this burden at a time that is crucial for their personal, psychological, and professional development

Effect of Vitiligo on Quality of Life, Assessed via DLQI Score



Vallerand IA. *J Am Acad Dermatol.* 2018; Baidya S, et al. *Ind Psychiatry J.* 2021.

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Psychological Burden of Vitiligo

- Vitiligo patients can experience a variety of psychological problems like depression, anxiety, sleep disturbance, adjustment disorder and dysthymia
- Risk of depression is higher in patients that were diagnosed prior to age 30
- Risk of depression diminishes as diagnostic age increases
- There are even studies showing that patients with depression could be at increased risk for subsequent development of vitiligo
 - Treatment with an anti-depressant is protective

Vallerand IA. *J Am Acad Dermatol.* 2018.

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Psychological Burden of Vitiligo



- In some countries, **vitiligo can be mistaken for leprosy or STI** which adds to stigma
 - Women in these countries can have difficulty getting married
 - In some religions, vitiligo can affect **“expectations for the destiny of the soul after death”**
- In some cultures, patients will be ostracized and unable to work, marry, or participate in social life



Vallerand IA. *J Am Acad Dermatol.* 2018; Ezzedine K, et al. *J Am Acad Dermatol.* 2019; Alikhan A. *J Am Acad Dermatol.* 2011.

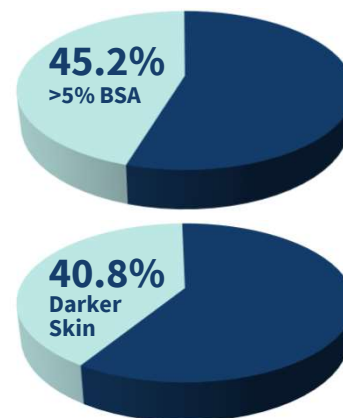
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The Global VALIANT Study (Vitiligo And Life Impact Among International CommuniTies)



- Qualitative, cross-sectional population-based study
- May 6, 2021 – June 21, 2021
- 3541 adults with vitiligo asked questions about their emotional well-being, including QoL and mental health
 - Range: 18-95 years, median 38 years
 - 54.6% were male
- Vitiligo Impact Patient scale (VIPs) scores
 - Range 0-60
 - Higher scores = more psychological burden

Key Patient Characteristics



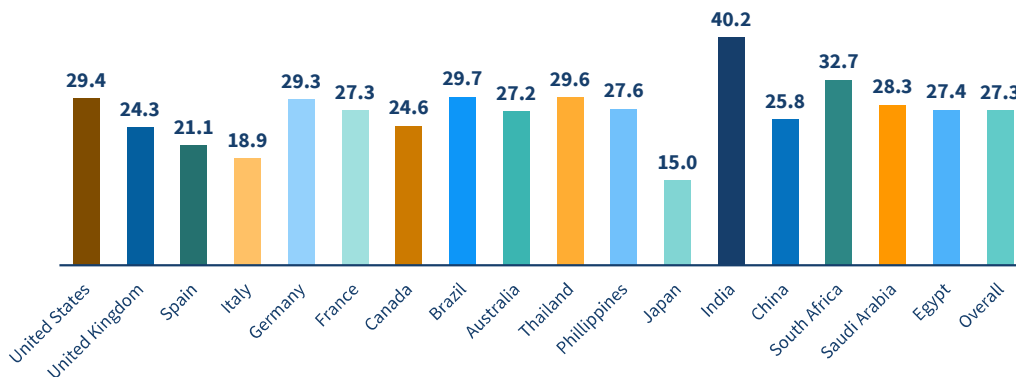
Bibeau K, et al. *JAMA Dermatol.* 2023.

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The Global VALIANT Study (Vitiligo And Life Impact Among International Communities)



VIPs Scores, by Geographical Area



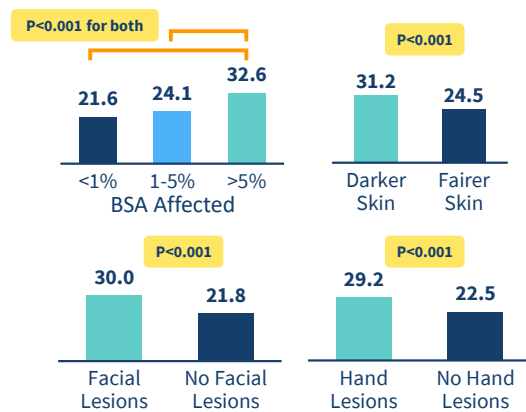
Bibeau K, et al. JAMA Dermatol. 2023.

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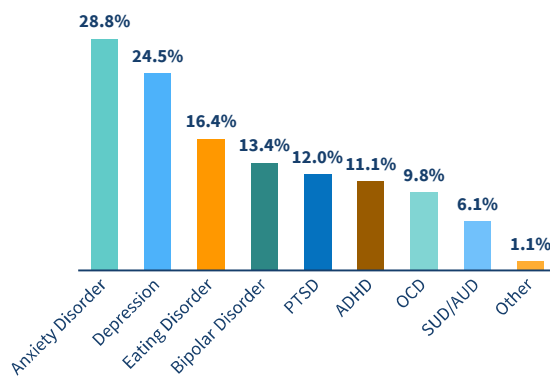
The Global VALIANT Study (Vitiligo And Life Impact Among International Communities)



VIPs Scores, by BSA, Fitzpatrick Skin Type, and Facial or Hand Lesions



Percentage of Individuals with Formal Mental Health Diagnoses



Bibeau K, et al. JAMA Dermatol. 2023.

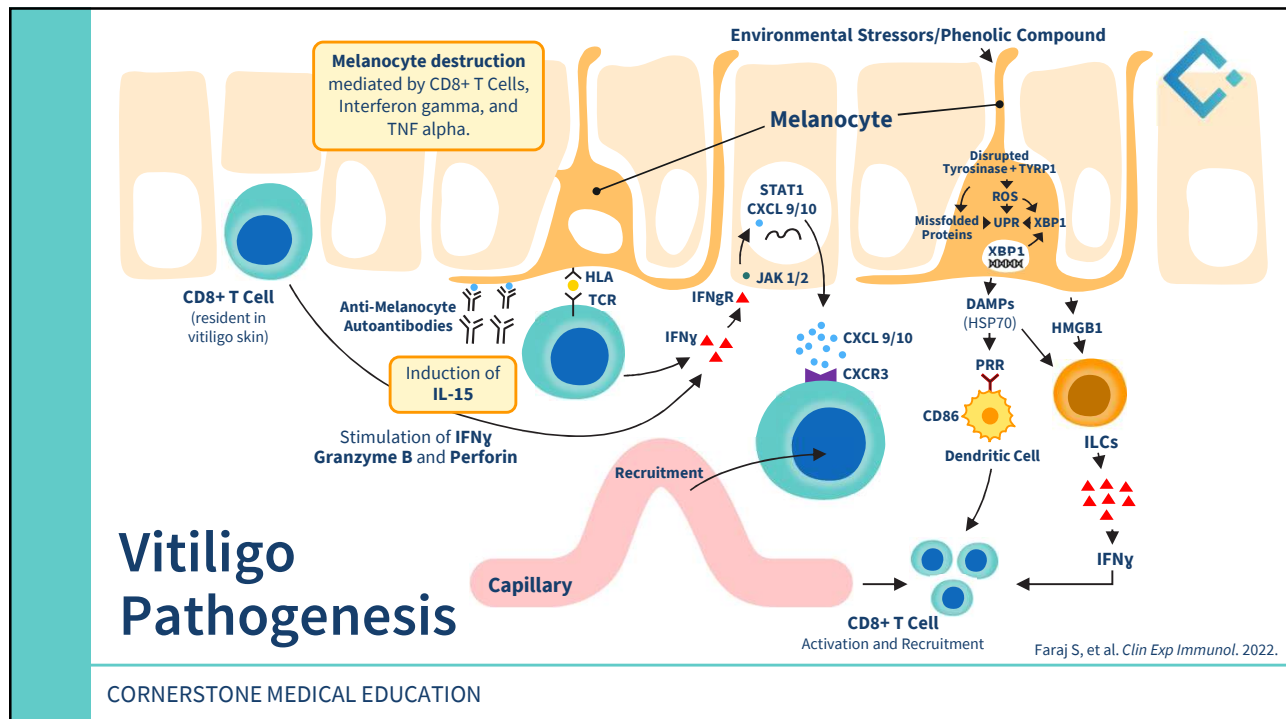
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State of the Science

Understanding Vitiligo Pathogenesis and Therapeutic Targets

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Vitiligo Triggers

- **Genetic Propensity** → often family history of vitiligo (25-50% of patients; 6% will have affected sibling) or other autoimmune diseases
- **Psychological Stress**
- **Drugs**
 - Imiquimod, Interferons, Nivolumab, Pembrolizumab, Ipilimumab, and Adalimumab
 - Induction of melanoma-associated vitiligo with Nivo, Pembro and Ipi is actually a positive indicator of therapeutic response
- **Oxidative Stress**
 - Exposure to environmental toxins, chemical agents and UV radiation
 - Overproduction of reactive oxygen species
- **Viral Infections/Vaccinations**
 - Could trigger activation of autoreactive CD8+/CD4+ T and B cells that can trigger autoimmune disease
 - Could also just be dysregulation of the CD8+ T cells amidst the storm of viral illness
 - CMV, EBV, HIV, and COVID-19 have all been reported to trigger vitiligo

Buckhair A, et al. *JAAD Case Rep.* 2022; Schmidt A, et al. *JAAD Case Rep.* 2022.

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Novel Approaches to Vitiligo Treatment

Moving Beyond Traditional Therapeutic Options

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Treatment Goals

Halt Progression

Repigment Skin

**Maintain
Repigmentation**

**Make Your Patient
Happy**

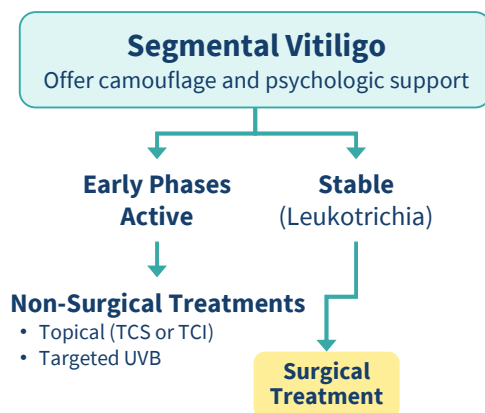
*“Clinicians should be aware that vitiligo is **not merely a cosmetic disease** and that there are **safe and effective treatments available** for vitiligo.”*

Rodrigues M, et al. *J Am Acad Dermatol.* 2017.

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Treatment Algorithm for Vitiligo

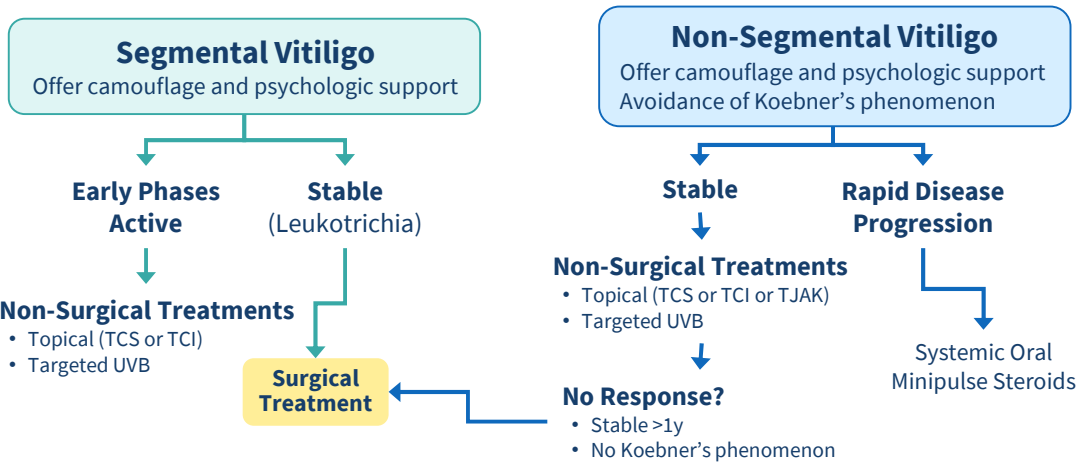


TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; UVB, ultraviolet B

Bergqvist C, et al. *Dermatology.* 2020.

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Treatment Algorithm for Vitiligo



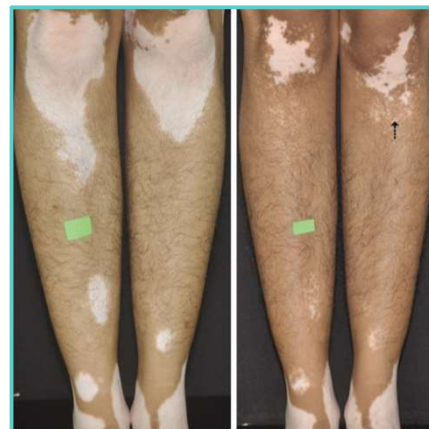
TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; UVB, ultraviolet B

Bergqvist C, et al. *Dermatology*. 2020.

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How Does Repigmentation Happen?

- Perifollicular- 55%
- Marginal- 5%
- Diffuse- 28%
- Combined
- Most Stable Repigmentation Pattern:
 - Marginal > Perifollicular > Combined > Diffuse
- Speed of Repigmentation:
 - Diffuse > Perifollicular



Parsad D, et al. *J Am Acad Dermatol*. 2004; Image from Narahari SR, Aggithaya MG. *Current Science*. 2016.

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Prognostic Indicators

Favorable Prognosis

- Younger patients
- Recent onset of disease
- Darker skin types
- Areas of involvement on face, neck, and trunk

Poor Prognosis

- Mucosal involvement
- Family h/o vitiligo
- Koebnerization
- Distal extremity involvement

Delbaere L, et al. *Dermatological Reviews*. 2022; Zhang L, et al. *JAMA Dermatol*. 2020; Sosa JJ, et al. *J Am Acad Dermatol*. 2015.

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Treatments

- Numerous treatment options exist but there is **no cure**
- **Early treatment is always more effective**

- Topical corticosteroids (TCS)
- Topical calcineurin inhibitors (TCI)
- Topical calcipotriene
- Topical JAK inhibitor
- Light therapy
- Pulsed dose oral corticosteroids
- Surgical modalities
- Depigmentation

+ New Treatments on the Horizon

Thawabteh AM, et al. *Molecules*. 2023; Diotallevi F, et al. *Int J Mol Sci*. 2023; Cunningham KN, et al. *Am J Clin Dermatol*. 2023.

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TCS (Topical Corticosteroids)

- Commonly used **first line**
- Can halt progression and induce repigmentation
 - **Complete repigmentation rates as high as 49%**
- Patients need to be followed and monitored for signs of atrophy
- More effective in kids compared to adults
- Head and neck areas have best response
- Work better if **combined with light therapy**
 - **Enhances repigmentation rate threefold** when combined
- Most commonly used:
 - Clobetasol once daily for body
 - Fluticasone once daily for face and folds

Patra S, et al. *J Am Acad Dermatol.* 2021; Radakovic-Fijan S, et al. *J Am Acad Dermatol.* 2001; Thawabteh AM, et al. *Molecules.* 2023; Diotallevi F, et al. *Int J Mol Sci.* 2023; Cunningham KN, et al. *Am J Clin Dermatol.* 2023.

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TCI (Topical Calcineurin Inhibitors)

- Tacrolimus (0.03, 0.1) and pimecrolimus
- Similar to slightly inferior results to topical steroids
- **Seemingly safer long term** than topical steroids
- Best results on head and neck
- **Mean repigmentation rates range from 26-73%**
- Works better when **combined with light**
 - Studies combining topical tacrolimus and excimer laser showed great efficacy

Lee JH, et al. *JAMA Dermatol.* 2019; Thawabteh AM, et al. *Molecules.* 2023; Diotallevi F, et al. *Int J Mol Sci.* 2023; Cunningham KN, et al. *Am J Clin Dermatol.* 2023; Bertolani M, et al. *Dermatol Reports.* 2021.

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TCS vs TCI

- One study (randomized, double-blind, comparative trial) looked at clobetasol 0.05% cream once daily vs tacrolimus 0.1% ointment twice daily in kids with vitiligo
- Clobetasol- 49% repigmentation
- Tacrolimus- 41% repigmentation
- But the difference was **not** statistically significant

Lepe V, et al. Arch Dermatol. 2003.

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Topical Calcipotriene

- **Inferior** to topical steroids and TCIs
- Can be used **adjunctively for steroid holidays**, etc.
- **No benefit** when combined with light therapy

“When combined with topical corticosteroids, repigmentation rates increase, the delay in the onset of repigmentation shortens, and there is a greater stability of repigmentation compared with either as monotherapy.”

Felsten K, et al. J Am Acad Dermatol. 2011.

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Topical Ruxolitinib

- Approved for patients age 12 and up to treat nonsegmental vitiligo
 - **First and only FDA approved topical treatment for repigmentation**
- Applied twice daily to up to 10% BSA
- Binds to JAK1/2 and inhibits Interferon Gamma signaling which reduces the CD8+ T Cell destruction of melanocytes
- TRuE-V1 and TRuE-V2 (phase 3 studies) showed efficacy in producing repigmentation, especially on the face
- **50% of patients achieved F-VASI75** over a year; **30% F-VASI90**
- Very tolerable

FDA Prescribing Information.

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Topical Ruxolitinib

- Note: <20% BSA for atopic dermatitis, <10% BSA for vitiligo
- **Black Box Warning:**
 - **Serious Infections:** Avoid use if active infection, including local infection
 - **Mortality:** Patients ≥ 50 y with ≥ 1 CV risk factor had higher rate of all-cause mortality vs TNFi
 - **Malignancy:** Lymphoma and other malignancies observed, with smokers at higher risk
 - **MACE:** Smokers at higher risk; D/C in patients with history of MI or stroke
 - **Thrombosis:** PE/DVT/arterial thrombosis
 - Patients ≥ 50 y with ≥ 1 CV risk factor had higher rate of thrombosis vs TNFi

FDA Prescribing Information.

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TRuE-V1 and TRuE-V2 Trials (Topical Ruxolitinib Evaluation in Vitiligo Study 1 and 2)



- Two phase 3, double-blind, vehicle-controlled trials
 - North America and Europe
- Age ≥12y with non-segmental vitiligo
 - Depigmentation <10% BSA

• 2:1 ratio

- 1.5% ruxolitinib cream
- Vehicle

Apply twice daily x 24 weeks

Option for all to apply ruxolitinib cream through week 52

• Primary Endpoint: F-VASI75 at week 24

- F-VASI: range 0 to 3, with higher scores indicating a greater area of facial depigmentation

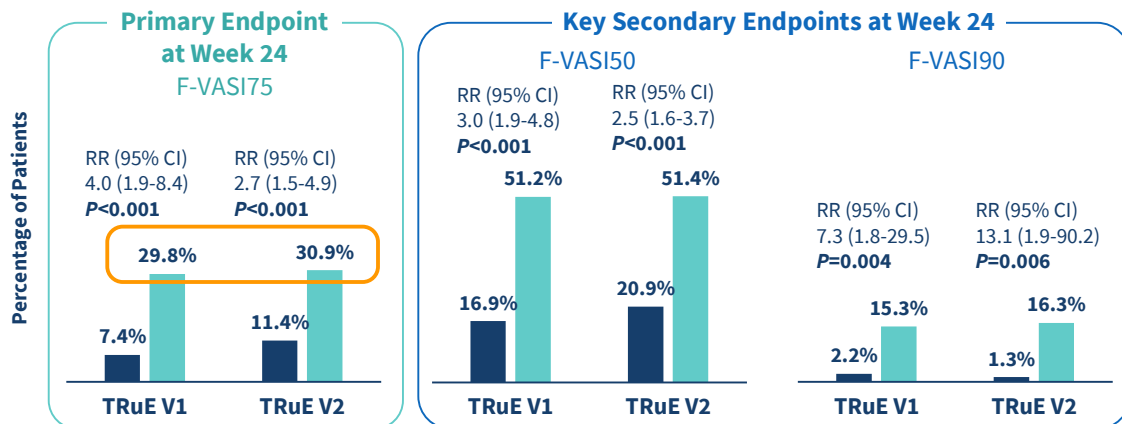
Rosmarin D, et al. *N Engl J Med.* 2022.

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TRuE-V1 and TRuE-V2 Trials (Topical Ruxolitinib Evaluation in Vitiligo Study 1 and 2)



■ Vehicle ■ Ruxolitinib 1.5%



Rosmarin D, et al. *N Engl J Med.* 2022.

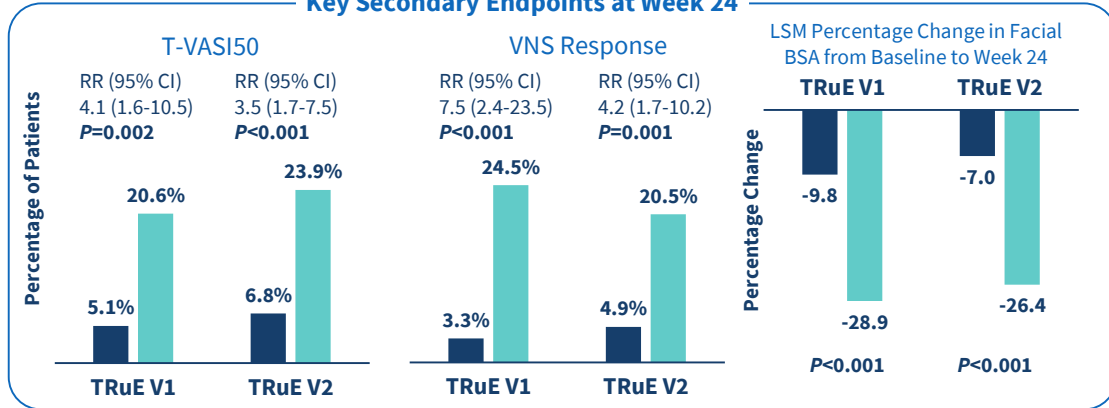
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TRuE-V1 and TRuE-V2 Trials (Topical Ruxolitinib Evaluation in Vitiligo Study 1 and 2)



■ Vehicle ■ Ruxolitinib 1.5%

Key Secondary Endpoints at Week 24



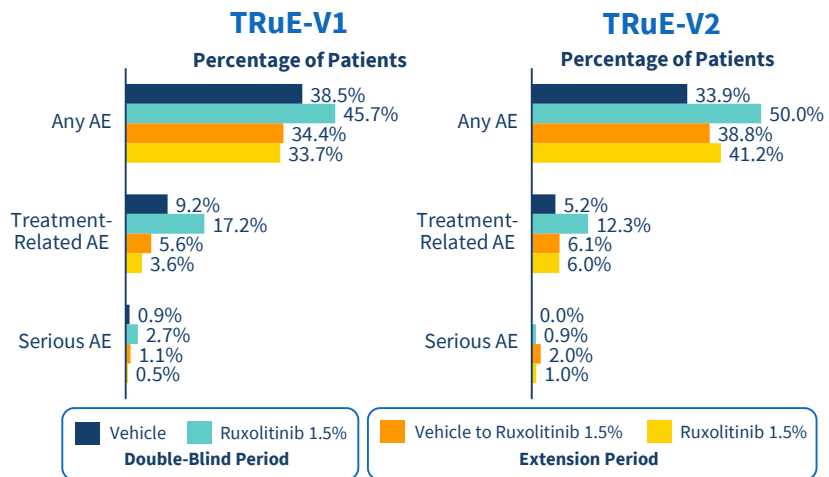
Rosmarin D, et al. *N Engl J Med.* 2022.

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TRuE-V1 and TRuE-V2 Trials (Topical Ruxolitinib Evaluation in Vitiligo Study 1 and 2)



- Ruxolitinib was well-tolerated
- Most common adverse events (AEs) over 52 weeks:
 - Application-site acne (6.3% and 6.6% in V1 and V2, respectively)
 - Nasopharyngitis (5.4% and 6.1%)
 - Application-site pruritus (5.4% and 5.3%)



Rosmarin D, et al. *N Engl J Med.* 2022.

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On the Horizon: Tapinarof



- Tapinarof is an aryl hydrocarbon receptor agonist
- MOA capable of suppressing immune response and inhibiting oxidative stress → seems like a good candidate to treat vitiligo
- Capable of inducing remission in psoriasis by reducing formation of memory T cells, it could possibly induce long lasting remission of vitiligo too
- Case reports of its benefit have been in the literature

Liu L, et al. *J Am Acad Dermatol Case Reports*. 2023.

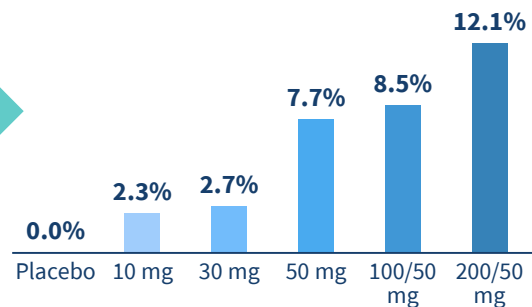
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On the Horizon: Oral JAK Inhibitors



- Case reports have been published showing benefit with oral tofacitinib and oral ruxolitinib
- Phase 2 b study of **oral ritlecitinib** →
- Other oral JAK Inhibitors are in the process of being evaluated to treat vitiligo

Percentage of Patients Achieving F-VASI75 by Week 24, by Placebo or Dose of Oral Ritlecitinib Administered



Ezzedine K, et al. *J Am Acad Dermatol*. 2023.

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Light Therapy

- Narrowband UVB (311 nm) > PUVA and broad band UVB
 - **PUVA really increases risk of NMSC and melanoma (as high as fivefold increase in melanoma)**
- Probably works by immunosuppressive and melanocyte stimulatory effects
- Narrowband UVB also induces tyrosinase (an enzyme essential for production of melanin)
- A good fit for extensive disease and rapidly spreading disease
- Can be difficult logistically (2-3 times/wk, often in office setting)
- **If it hasn't worked within 6 months, it won't work**

Mohammad T, et al. *J Am Acad Dermatol.* 2017; Garza-Mayers AC, et al. *J Am Acad Dermatol.* 2023.

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Narrowband UVB Therapy for Vitiligo

4 Months



6 Months



14 Months



https://www.umassmed.edu/globalassets/vitiligo/compare/before_10.jpg

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Light Therapy: Excimer Laser

- Xenon Chloride Monochromatic Laser that emits at 308 nm
- More focused on the spots
- Doesn't create increased tanning on the normal skin
- Works better in combination with topicals (steroids or TCIs)
- Can be particularly nice for segmental vitiligo (best when done early in the course)



<https://images.squarespace-cdn.com/content/v1/5ac6c106a2772c5ffa1b584c/1591120459687-6M13FM196UJIYGSSQ56E/excimer-before-after.jpg>

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Heliocare (Polypodium Leucotomos)

- OTC supplement
- Derived from a fern leaf extract from south/central America
- 1 pill PO daily in the morning before sun exposure
- Used to protect the skin from the sun but also, interestingly, makes light therapy work better
 - Fewer treatments required, repigmentation occurs faster

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Oral Pulsed Dosed Steroids

- Most effective at stopping rapidly spreading vitiligo
 - **Can halt disease progression in 88-92% of patients with active disease**
- Dexamethasone 4 mg or Betamethasone 5 mg 2 consecutive days a week x 12-24 weeks
- **Stops progression in about 90% of patients**
- *Does not tend to provide benefit in repigmentation*
- Well tolerated, no evidence of suppression of endogenous cortisol production
- Tends to work well with light therapy

Patra S, et al. *J Am Acad Dermatol*. 2021.

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Surgical Modalities

- Avoid in patients with features of the Koebner phenomenon
- **Patients must have STABLE, NON-RESPONSIVE vitiligo**
 - Stable for **at least 12 months**
- Face and neck lesions do the best
- Sometimes people will treat after the surgery with light therapy and/or tacrolimus 0.1% ointment to potentially improve benefit

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Surgical Modalities

- **Suction Blister Grafting**
 - Flexor arm is great source site
 - Induce a blister with pencil eraser and then unroof the blister and transplant to the affected areas (which you also suction blister to prepare it for adherence and uptake)
 - Tang et al has a great article on how it's done
- **Punch Grafting**
 - Multiple teeny PGs are harvested and placed on the affected site
 - Boersma et al has great article on how it's done
- **Split-Thickness Skin Graft**
 - Can cover larger areas
 - Requires anesthesia (requires a dermatome to harvest tissue)

Kim J, et al. *J Am Acad Dermatol*. 2023.

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Maintenance of Repigmentation

- After repigmentation, there is a 30-40% chance of recurrence
- Using topical tacrolimus 0.1% can reduce that chance to around 5-10%
 - Apply bid 2 days a week

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Depigmentation

- Patients with recalcitrant and widespread vitiligo might choose this option
- Monobenzylether of hydroquinone (MBEH) 20%- FDA approved for depigmentation
- Applied twice daily x 4-12 months
- Strict sun avoidance
- Permanent

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Practical Considerations for Managing Vitiligo

Combining the Latest Data and Shared Decision-Making Strategies to Determine Treatment

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Case Discussion

- 13 year old female presents for evaluation of some “light skin spots”
- They started to appear about a year ago
- Upon exam, you see depigmented macules and patches that accentuate with wood’s lamp on her face, knees, ankles, underwear area and forearms
- You also notice that there is “confetti-like” depigmentation on her knees and forearms
- What treatment options would you discuss with her and her family?



Case Discussion

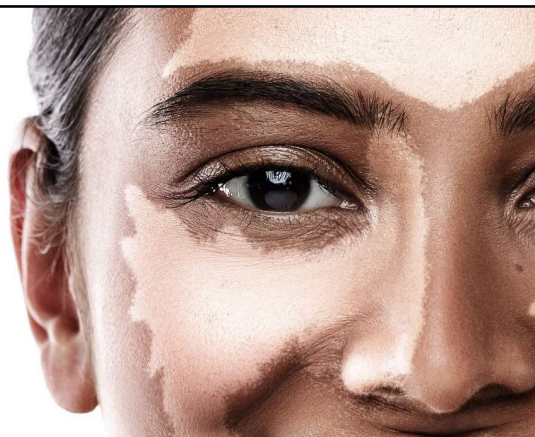
- 6 year old boy presents with a 6 month history of depigmented macules and patches on his face
- Upon exam, the depigmentation is limited to one segment on the left side of his face
- What would you tell this patient and his family about this type of vitiligo?
- What treatment options would you consider?



Case Discussion

- 22 year old female presents with a several year history of vitiligo
- In the past, she has tried topical steroids and a topical calcineurin inhibitor with minimal success
- She saw a commercial for a new topical cream for vitiligo and she wants to try it
- What would you tell her about topical ruxolitinib?

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