

## Disorders of Pigmentation

Maui Derm NP+PA  
June 2022

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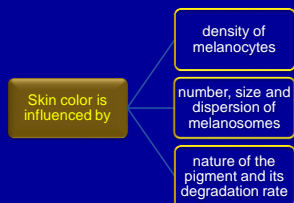
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## Disclosures

- Consultant: Galderma Laboratories, LP, Almirall, Femdale Laboratories, Inc., Gore Range Capital, Bristol-Myers Squibb, AbbVie Verrica Pharmaceuticals, Inc., UCB, Ortho
- Speaker: Pfizer Inc.
- Board Member or Executive: Foundation for Research & Education of Dermatology Dermavant Sciences, Womens Derm Society
- Contracted Research: AbbVie, Incyte Corporation, Dermavant Sciences, Inc., AOBiome, LLC
- Ownership Interest: Gore Range Capital
- Other Financial Relationship: National Psoriasis Foundation

2

## Melanin



3

## Melanin Distribution

- Untanned skin: localized in the basal layer of epidermis
- Tanned skin: distributed throughout the skin

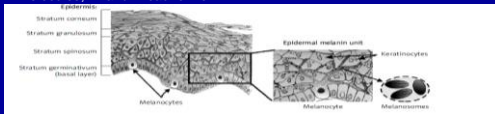
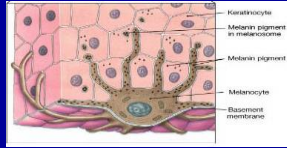
2,000 melanocytes /mm<sup>2</sup>  
900-1,500 melanocytes /mm<sup>2</sup>



4

### Melanocyte

- Mature melanocytes: oval or fusiform dendritic cells, smaller than keratinocytes.
- Each melanocyte is bound to 30-40 keratinocytes with help of adhesion molecules, E- and P-cadherins.



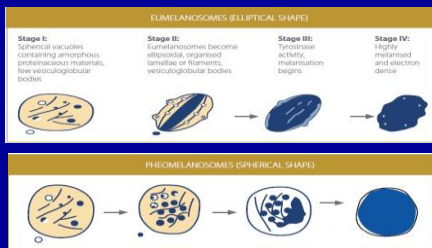
5

### The 4 Steps of Melanogenesis

1. Biogenesis of melanosomes
2. Intracellular transport of melanosomes
3. Melanosome transfer into keratinocytes
4. Melanosome distribution and degradation

6

### Stages of Melanosome Maturation



7

### Hyperpigmentation

- Hyperpigmentation is characterized by the darkening of an area of the skin caused by the overproduction of a pigment known as **melanin**.
- Hyperpigmentation in the skin can result from:
  1. Increased production of the melanin pigment, or pigment incontinence.
  2. Accumulation of a large number of melanocytes.
  3. Deposition of other (non-melanin) pigments or substances in the skin.



8

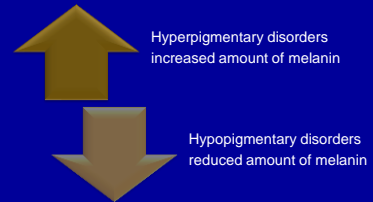
## Differential Diagnosis of Hyperpigmentation

**Table 1. Differential Diagnosis of Hyper- and Hypopigmentation**

Hyperpigmentation	Hypopigmentation
Postinflammatory hyperpigmentation (acne, psoriasis, atopic and contact dermatitis, lichen planus, trauma, drugs, and fixed-drug eruptions)	Acquired (common)
Melasma	Vitiligo
Solar lentiginos	Pityriasis alba
Ephelides (freckles)	Tinea versicolor
Café-au-lait macules	Postinflammatory hypopigmentation
Nevi	Congenital (uncommon)
Melanoma and precursors	Albinism
	Piebaldism
	Tuberous sclerosis
	Hypomelanosis of Ito

9

## Hyperpigmentary Disorders



10



11

## Melasma

- Treatment Options
  - Topical Retinoids & Combination Therapy
  - Azelaic Acid
  - Hydroquinone
  - Chemical Peels
  - Cosmeceuticals
  - Lasers
  - Dermabrasion
  - Reassurance and Time

12

## Triple Combination Therapy

- Multicenter RCT of Southeast and East Asian patients
- 260 patients → 129 in Triple combo group
- 260 patients → 131 in Hydroquinone only group
- 8 weeks treatment
- Assessed by Melasma GSS, MASI, patient satisfaction
- Triple combo had superior efficacy to monotherapy in GSS and other variables but more adverse effects

Chan R et al. BJD 2008

13

## Hydroquinone Safety

- The supervised use of prescription topical hydroquinone had no more than a theoretical risk of malignancy, developing ochronosis or other long term safety side effects
- No substantial evidence to prove its carcinogenicity
- TAKE THE TIME TO DISCUSS LONG TERM USE WITH EACH OF YOUR PATIENTS !!

Nordlund JJ, Grimes PE, Ortonne Jp. JEADV 2006; 20:781-7

14



15

## Hydroquinone Safety

- Hydroquinone remains the gold-standard, and non-HQ based therapies remain second line and/or adjunctive

16

## Azelaic Acid

- Dicarboxylic acid that has selective cytotoxic effects
  - Inhibits tyrosinase and mitochondrial respiratory enzymes
- 20% azelaic acid was used twice daily in approx 132 patients with facial melasma
- 73% had improvement after 6 months of therapy
- Minimal side effects of erythema, pruritus, and mild burning

Verrallo-Rowell VM et al. Acta Derm Venereol Suppl. 1989;143:58-61

17

## Kojic Acid

- Produced by *Aspergillus oryzae*
- Tyrosinase inhibitor and photo protective effect
- More clinically stable molecule but with weaker lightening properties
- Comparative study showed that Glycolic Acid with kojic acid and Glycolic acid with hydroquinone were effective in treatment of melasma

Garcia A et al Dermatol Surg 1996; 22:443-7

18

## Vitamin C

- Reduces tyrosinase activity via antioxidant effect
  - Stable derivate called MAP (magnesium-ascorbyl-phosphate)
- 5% ascorbic acid vs 4% hydroquinone studied
- 62.5% vs 93% improvement, but 6.2% with SE's vs 68.7%
- Although HQ showed better response, Vit C less irritating
- Use in combination therapy +/- HQ

Espinal-Perez LE et al. Int J Dermatol. 2004;43:604-7

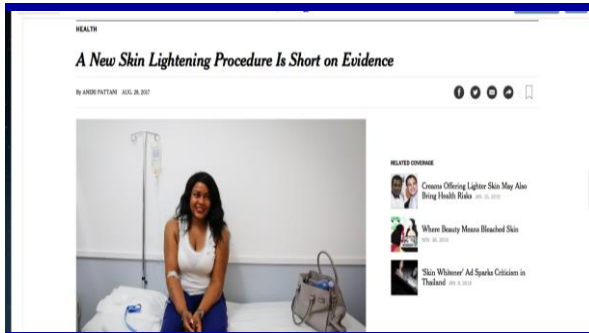
19

## Glutathione

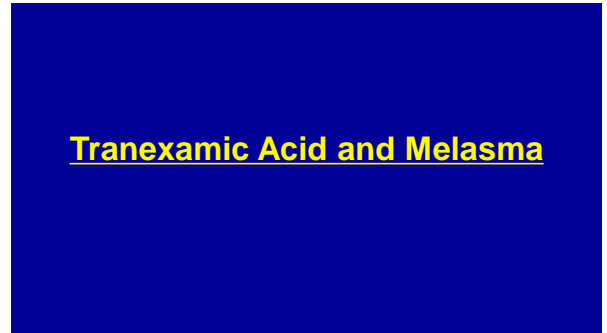
- Potent antioxidant → indirect inactivation of tyrosinase
  - Assists in converting eumelanin → to pheomelanin
- Typically used orally
  - Also being given IV in Asia.
- Still controversial due to bioavailability, but some promising results in studies

Allen J et al. J Altern Complement Med 2011; 17:827-33

20



21



22

## Tranexamic Acid

- Fibrinolytic agent
- Inhibits plasminogen activator
  - Less arachidonic acid → less prostaglandin → less tyrosinase activity
- Ultimately, reducing pigment

23

## Tranexamic Acid

- Contraindications
  - Current/past DVT/PE/clotting disorder/anti-coagulant medications
  - Pregnancy/Breastfeeding
  - Smoking
  - Renal/Cardiac/Pulmonary disease
- Dosing
  - Most effective dosing seems to be at 500mg daily
  - Topical, oral, and intradermal forms

Tse TW, Hui E. Tranexamic acid: and important adjuvant in the treatment of melasma. J Cosmet Dermatol. 2013 Mar;12(1):57-66.

24

## Topical tranexamic acid to treat pigmentation

Tranexamic acid has recently been introduced as a topical therapy aimed to reduce pigmentation in melasma, post-inflammatory hyperpigmentation (PIH), and hyperpigmentation

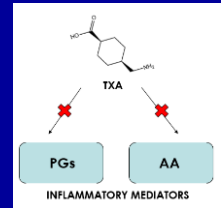


The TSC, Inc. © 2018. Tranexamic acid as an effective treatment in the treatment of melasma. J Clin Cosmet Dermatol. 10(1):17-26.  
 The TSC, Inc. © 2018. Tranexamic acid as an effective treatment in the treatment of melasma. J Clin Cosmet Dermatol. 10(1):17-26.  
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25

## Tranexamic acid mechanism of action in treating pigmentation

TXA controls pigmentation by inhibiting the release of inflammatory mediators, specifically prostaglandins and arachidonic acid, which are involved in melanogenesis

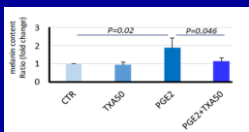


The TSC, Inc. © 2018. Tranexamic acid as an effective treatment in the treatment of melasma. J Clin Cosmet Dermatol. 10(1):17-26.

26

## TXA mechanism of action In vitro assessment

Human Epidermal Melanocytes (HEM) Model



Tranexamic acid (TXA) inhibits PGE2-induced melanin production in Human Epidermal Melanocytes (HEM)

- **Protocol:** A 10-day, in vitro study. PGE2-induced melanin production in human epidermal melanocytes (HEM) from 4 donors treated with tranexamic acid.
- **Results from this study validated:**
  - PGE2 stimulates melanin production in HEM
  - TXA inhibits melanin content in PGE2-stimulated melanocytes
  - TXA does not influence the pigmentation in unstimulated HEM

27

## Chemical Peels & Melasma

28

## Peels in Melasma

- Glycolic Acid 30-50% → 5-6 peels q2-3 weeks
- Salicylic Acid Peels 15-30% → 5-6 peels q2-3 weeks
- Trichloroacetic Acid Peels 10-15%
  - Can prime skin with Glycolic and then follow with TCA
  - Although, commonly use 10-15% in Types IV-VI

29

## Vitiligo

- TREATMENT OPTIONS
  - Topicals including steroids, vit D analogues, calcineurin inhibitors
  - Depigmentation
  - Systemic tx
  - Phototherapy
  - Surgical Treatment
  - Psychological Therapy
- IF TREATMENTS FAIL → ANALYZE PATIENT'S DESIRES

30

## Let's try to define!

- Active/Unstable Vitiligo
  - Depigmentation spreading more than 2% BSA in one month
- Chronic Vitiligo
  - Depigmentation present for at least 1 year with no h/o spontaneous repigmentation
- Refractory Vitiligo
  - Disease that is poorly responding to therapy → <25% repigmentation

31

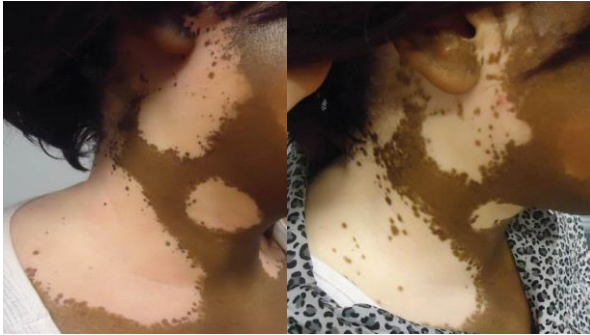
## Stabilizing Vitiligo

- Systemic Steroids
  - Oral Mini-Pulse Therapy (OMP)
    - Dexamethasone 4mg daily on 2 consecutive days per week
      - i.e Saturday and Sunday
    - Half the dose in children less than 16 years of age
  - Must counsel patients on side effects

Parsiad D, De D. Corticosteroid minipulses. In: Vitiligo. 1st ed. New York: Springer, 2010.p.319-24.  
 Pandya et al. DermQuest. <https://www.dermquest.com/expert-opinions/.../systemic-corticosteroids/>

32





33

## Stabilizing Vitiligo

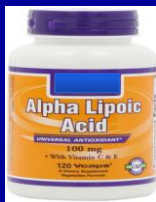
### •What I do

- IM Triamcinolone Acetonide 60mg qmonth for 3 months
- Transition to Oral Mini-Pulse Therapy (OMP), if still spreading
  - Dexamethasone 4mg daily on 2 consecutive days per week
- Have the patient on a traditional therapy
- Start patient on Calcium/Vitamin D supplement

34

## Antioxidants in Vitiligo

- Number of studies support the use anti-oxidants
- Especially in combination with phototherapy (NB-UVB)
- Alpha Lipoic Acid, Vit E, Vit C



Dell'Anna ML et al. Clin Exp Dermatol. 2007 Nov;32(6):631-6.

35

## Antioxidants in Vitiligo

- 28 Pts with non-segmental vitiligo
  - 2 months before and for 6 months during the NB-UVB treatment
  - 47% of pts > 75% repigmentation vs.18% in placebo group
  - Improvements in catalase activity, decrease in overall ROS production
- Oral antioxidants containing alpha-lipoic acid combined with NB-UVB enhanced repigmentation by reducing oxidative stress

Picardo M et al. Clin Exp Dermatol, 2007 Nov;32(6):631-6

36

## Antioxidants in Vitiligo

- ***Polypodium Leucotomas***
  - NBUVB 2x weekly
  - Treated with PLE 250mg TID vs placebo for 26 weeks
  - Higher repigmentation of head and neck region in test (44%) vs placebo group (27%) [ $P = 0.06$ ]
    - Other sites with limited repigmentation

Middlekamp-Hup MA et al. *JEADV*. 2007;21:942-950

37

## Tacrolimus in Vitiligo

- Can use tacrolimus in combination with NBUVB
- Caution in pediatric population and long-term use
- Consider using 0.03% on face once daily and 0.1% on body

Fai DT, Cassano N et al. *JEADV*. 2007 Aug;21(7):916-20.  
Narrow-band UVB phototherapy combined with tacrolimus ointment in vitiligo: a review of 110 patients.

38

## Janus Kinase Inhibitors for Vitiligo



Craiglow BG et al. *JAMA Dermatol*. 2015;151(10):1110-1112

39

## Topical JAK Inhibitors for Vitiligo

- Ruxolitinib 1.5% cream BID
- Change in VASI score from baseline to week 20
- 23% improvement -- 11/12 patients
- Adverse Events
  - Erythema
  - Hyperpigmented rim at edge
  - Papular Eruption
  - Labs only at baseline

\*Journal of the American Academy of Dermatology 2017 76, 1054-1060.e1DOI: (10.1016/j.jaad.2017.02.048)

40



41



42

**Repigmentation in vitiligo using the Jans kinase inhibitor tofacitinib may require concomitant light exposure**

LUCY Y. LIU, BA,\* JAMES F. STIMMER, BS,<sup>†</sup> MAGGIE A. BELLA, MS,<sup>†</sup> JOHN E. HARRIS, MD, PhD,<sup>†</sup> and PAUL A. BEGG, MD, PhD<sup>†</sup>  
New Haven, Connecticut, and Worcester, Massachusetts

Before After

A

Before After

B

Liu et al.  
JAAD.  
October  
2017, pp.  
675-682

43

**Newer Vitiligo subtypes**

44



45

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**Confetti-like depigmentation: A potential sign of rapidly progressing vitiligo**

Juan Jesús Sosa, BS,<sup>1</sup> Sharif D. Currimbhoy, MD,<sup>2</sup> Uzoamaka Ukoha, BS,<sup>2</sup> Samantha Sirignano, BS,<sup>3</sup> Ryan O'Leary, MD,<sup>4</sup> Travis Vandergriff, MD,<sup>2</sup> Linda S. Hyman, PhD,<sup>5,6</sup> and Amit G. Pandya, MD<sup>7</sup>  
*Dallas, Texas, and Los Angeles, California*

Sosa et al. J Am Acad Derm. Vol 73, Number 2, 2017, pp. 856-862

46



47



48

## Trichrome Vitiligo

- Trichrome vitiligo is a variant of active vitiligo
- Describes lesions that have a tan zone of varying width between normal and totally depigmented skin, which exhibits an intermediate hue
- Histopathology shows vacuolar dermatitis
  - Often within the normal skin, and decreasing melanin granule density as you progress through the "zones"
- Majority of patients who have this, have non-segmental vitiligo vulgaris
- Early phototherapy, specifically PUVA in the studies, show good success

49



50



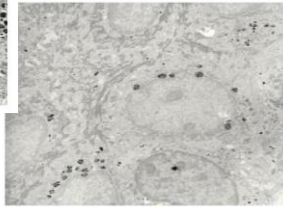
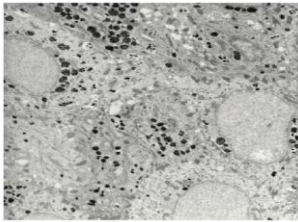
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51

## Progressive Macular Hypomelanosis

- Typically in females and darker skin patients
- Decrease of melanin noted via smaller numbers of type 2/3 melanosomes
- Postulated to be relate to *Propionibacterium spp.*
- Some case reports that it worsens in Pregnancy
  - Hormonal Theory vs Infectious

52



53

## Progressive Macular Hypomelanosis

- Some cases reports suggest PUVA as a treatment
- Benzoyl Peroxide topically in solution form from 5-10% has been the most reported
- Off label use of –cycline based antibiotics also possible
- What do I do in my clinic??
  - Topical BPO
  - Orals
  - Narrowband UVB 2-3 x week

54



55

## Support & Research

- [www.globalvitiligofoundation.org](http://www.globalvitiligofoundation.org)
- On Facebook, VITFriends Vitiligo Support Group
- Skin of Color Society
- Write to your Elected officials
- Attend the AAD/A Legislative Conference in September!

56

**Questions / Comments**

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57