Medical treatments for facial pigmentation

What’s new?

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Disclosures

- Research grants and/or honoraria:
  - Bioderma
  - Beiersdorf
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  - L’OREAL
  - ISIS Pharma
  - ISDIN
  - Pierre Fabre
  - SVR
  - Symrise
Pigmentation and photoprotection: What’s new?

• Visible Light induced pigmentation:


Study of the effects of UVA1 and Visible Light in healthy volunteers
Visible Light source: Halogen source 400-700nm High energy

- Visible light induces a hyperpigmentation in skin type IV to VI
- No pigmentation in fair skins
- Pigmentation more intense and more prolonged as compared to UVA1


Natural Sun exposure. India, Bengalore, Exposure to VL is obtained by blocking UV with physical filters.
Exposures: 8-32 min corresponding to VL 30-120J/cm² and UV 2-8 J/cm²

- Solar Visible light induces a hyperpigmentation in skin type IV to VI (Indian volunteers)
- Complementary effect of UV and Visible Light
Blue-violet light is responsible for hyperpigmentation induced by VL

Pro-pigmenting
Differentiation of melanocytes (in vitro)
No effect on pigmentation (in vivo)

Pigment Cell Melanoma Res. 2014;27:822-6
Blue light induces pigmentation

*Irradiation 415nm*

24h  7d  14d  21d

<table>
<thead>
<tr>
<th>10</th>
<th>60</th>
<th>120</th>
<th>1/ cm²</th>
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<tbody>
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<td>30</td>
<td>90</td>
<td>150</td>
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Rapid and long-lasting pigmentation

*p53 staining*

control  415nm  UVB

Cellular damages are mainly produced by UVB

Pigment Cell Melanoma Res. 2014;27:822-6
Shorter wavelengths of visible light impact skin pigmentation

- Propigmenting role of the visible light in skin types III and higher
- Blue-violet light is propigmenting / red light has no or weak effect on pigmentation
- Propigmenting doses of blue light correspond to ‘physiological’ exposures (1h30 during summer)
- Mechanisms involved differ from UV-induced pigmentation

➢ What are the mechanisms involved?
➢ Role in pigmentary disorders?
Visible light

Membrane of skin type III to VI melanocyte

OPSIN 3

400nm - 465nm

Ca^{2+}

Ca^{2+}

p38

CaMKII

CREB

USF1

MITF-M

USF1

MITF-M

Tyrosinase

DCT

TYRP1

J Invest Dermatol. 2018;138:171-178

Prolonged melanogenesis
Can Blue Light from Screens induce hyperpigmentation?

➢ HEV in solar light

- Solar intensity at ground level: 1000 W/m² (ASTM Standard, 2008).
- 45% corresponds to VL (400-700 nm): energy of VL = 450 W/m²
- HEV (400-450 nm) = 6.3 mW/cm²
- Pigmentary dose = around 1 h 30 - 2 h 30 sun exposure summer

➢ HEV/ Blue Light from Screens

- Low intensity emission: around 30 µW/cm²
  ➢ Several days/ nights (more than 150 h to achieve the minimal pigmentary dose)
- Reciprocity law not demonstrated

<table>
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<tr>
<th>Wavelength / nm</th>
<th>Table values (mJ/cm²/mn)</th>
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<tbody>
<tr>
<td>380 – 500 nm</td>
<td>415 nm</td>
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<tr>
<td>Iphone</td>
<td>2.26E-01</td>
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<tr>
<td>Computer screen</td>
<td>1.01E+00</td>
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*J Derm Science. 2019;92:69-70*
Additive effects of long wave UVA and visible light

➢ Optimal sunscreen requires longwave UVA and visible light protection

*Br J Dermatol.* 2018;178:1173-1180
Can we protect against visible light-induced pigmentation?

- **Visible Light / HEV protection**: physical solutions
  - Iron oxides or pigments to prevent VL/HEV induced pigmentation

*In vivo*

Products containing Titanium Dioxide, Red Iron Oxide, Yellow Iron Oxides, Black Iron Oxides in different proportions.

Four daily exp (144 J/cm² VL = 1 h sun exposure)

Solar simulator delivering VL 400-700 nm

Pigmentation prevention:

« D » > « A » = « B »

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Photodermatol Photoimmunol Photomed. 2017 33:260-266
Visible Light / HEV protection: who is concerned?

- Melasma
- PIH
- Acne marks
- Post Procedure
- Other PIH
- Other sun spots
- Sun induced pigmentation
- Melano competent individuals (FPT ≥ III)
- Pigmentary disorders
- PIH post peeling

PT IV

PT VI
Impact of protection against shorter wavelengths of visible light in melasma relapses

- Monocentric randomized comparative study on 40 patients with melasma
- Begin of the study the two first weeks of April
- End of the study the two first weeks of September
- Evaluation on MASI performed on standardized pictures (VISIA, Canfield) by two independent physicians blinded to the sunscreen received

No lost to follow-up
No significant differences in the quantity of sunscreen used

Interest of combining protection against UVB, UVA and shorter wavelengths of visible light for optimal protection in melasma

Δ in mean MASI score between last and first visit

* p<0.05

J Am Acad Dermatol. 2015;72:189-190
Photoprotection: FOCUS ON VISIBLE LIGHT AND PIGMENTATION

- **Visible Light / HEV protection**: clinical efficacy on cutaneous hyperchromias (sun spots)

  **Influence of visible-light on cutaneous hyperchromias: clinical efficacy of broad-spectrum sunscreens**
  - Population: 40 subjects with « small brown macules similar to solar lentigos » phototype II-III
  - Real Life exposure conditions.
  - 2 groups of solar protection: SPF 30 vs SPF30 + VL (iron oxide)
  - Evaluations: Confocal - Mexameter – self assessment – clinical evaluations (photo)
  - Study duration: 2 months (60 days)

Conclusions: Protection UV+VL > Protection UV only on Melanin index, epidermal pigmentation, melanin accumulation and percentage of hyperpigmentation area after 60 days (confocal)

*Photodermatol Photoimmunol Photomed. 2018 Jan 30. doi: 10.1111/phpp.12377*
The role of ambient light in PIH development

Rational:
- Sun exposure is known to increase PIH development, with a high prevalence in higher skin phototypes
- Inflammation is known to activate melanocytes and melanogenesis through several mediators (Leukotrienes, prostaglandins, interleukins, ...)

Do low doses of ambient light (Low UV amount + Visible light) contribute to the development of PIH?

Study design:
- **N=10 volunteers**
  - Age: 18-35
  - Skin type IV-V
- ITA 28° / -10°

Visual examination
- TEWL
- Colorimetric measures

Histology
- HES/FM
- Immunostainings
  - TYR, MITF, Col IV

Pigment Cell Melanoma Res. 2018;31:649-652
The role of ambient light in PIH development

PIH Characteristics at Day 29
- Complete wound healing
- Vascular proliferation/Hyperplasia
- Inflammatory infiltration
- Epidermal melanosis
- Melanin leakage /Dermal melanin
- Melanin within melanophages (CD68+)
- Active melanocytes with increased dendricity

PIH model validation

Pigment Cell Melanoma Res. 2018;31:649-652
The role of ambient light in PIH development

- Low doses of ambient light are sufficient to induce PIH
- Areas completely protected from any radiation using an opaque dressing do not develop PIH

Pigment Cell Melanoma Res. 2018;31:649-652
Conclusions

- Wavelengths of solar radiations beyond UVB have an impact on skin: UVA and VL
- Blue light stimulates a potent and prolonged hyperpigmentation in skin types III and higher
- Melanocytes sense blue light through OPSIN 3
- Blue light participates to the induction of PIH and to melasma relapses

Optimal photoprotection to prevent hyperpigmentation should cover UVB, UVA2, UVA1, Blue Light
How to treat post inflammatory hyperpigmentation?
Prevention of PIH

• Avoid procedure during summer period
• Be very careful if personal history of PIH or in individuals with Asian ancestry

• Without risk factor
  • Before the procedure:
    • Temporary resting of melanocytes using strict photoprotection at least the 15 days before the procedure
  • After the procedure:
    • At best, opaque dressing for at least 15 days
    • If opaque dressing impossible, use sunscreen offering the best UVB, UVA and VL protection
Prevention of PIH

• If risk factor:
  • Before the procedure:
    • Temporary resting of melanocytes using strict photoprotection at least the 15 days before the procedure
    • Discuss 4% HQ for the 15 days before the procedure
  • After the procedure:
    • At best, opaque dressing for at least 15 days
    • If opaque dressing impossible, use sunscreen offering the best UVB, UVA and VL protection
    • Use potent topical steroids for 15 days
Treatment of PIH

- Photoprotection using sunscreen offering the best UVB, UVA and VL protection
- Kligman’s duo (4% HQ + potent topical steroid) up to 4 months if needed
- Use of tranexamic acid reported in early stages of PIH but need to be confirmed

- If late PIH or PIH resisting to Kligman’s duo, discuss test session with QS or PicoS laser
  - Sometimes good results
  - But risk of failure or worsening, to be discussed with the patient
How to treat lichen planus pigmentosus?

- No treatment truly effective...
- Open label prospective study of 32 patients
- Oral isotretinoin 20mg/d for 6 months + sunscreen
  - 27 patients completed the study
  - Improvement:
    - Good: 22%
    - Moderate: 56%
    - Mild: 6%
    - None: 16%
  - Action on pruritus
  - Better in early stages
MELASMA

- Brown or bleu-grey macules
- Face
- Bilateral, symmetrical
- Irregular geographic borders

Skin disorder affecting the melanocytes

3 main factors:
- Genetic
- UV
- Hormonal status
Revisiting melasma pathology

Increased number of melanocytes, increased epidermal and dermal melanin

- 93% moderate/severe elastosis
- 84% increased melanocytes
- Increased melanin at all level of the epidermis
- Dermal melanin in 36% with increased dermal melanin and melanophages (12%)

- 70% mild/moderate elastosis
- No increase in melanocytes
- Melanin not increases in the epidermis
- Dermal melanin noted in 36% of perilesional cases in Korean skin
Melasma, a vascular disorder?

Vessel size (µm²)

Factor VIIIa-related antigen

Perilesional normal skin

Vessel density (mm²)

Factor VIIIa-related antigen

Lesional skin

Vessel area (%)

C

D

E

Normal       Lesion                          Normal       Lesion                          Normal       Lesion

P=0.001

P=0.008

P=0.001
Fibroblast-secreted factors are involved in melasma pathophysiology

Crucial role of the Wnt pathway in the regulation of pigmentation by the fibroblasts
Role of skin microvascularization in pigmentation

- 100 benign vascular lesions
- High magnification digital dermoscopy (x50 – X200)
- Laser confocal microscopy and histology

Significant increase of pigmentation above and around vascular lesions
Crucial role of endothelin 1 secreted by endothelial cells
ET1

Control

EDNRb inhibitor

-  +

HMVEC

Control

EDNRb inhibitor

-  +

HMVEC

Control

EDNRb inhibitor

-  +

HMVEC

Melanocyte

Endothelial cell

ET1

EDNRb

ERK

P

MITF

DCT

TYR

p38

Pigmentation

Mechanism of action of tranexamic acid in melasma?

- Prospective study with biopsies after 12 weeks of treatment with TA

- TA might act on melasma through a decreased production of endothelin 1

Mélasma = UVB + UVA + Blue light
+ pigmentation
+ vascularization
+ elastosis and fibroblast secreted factors
+ altered basal membrane

=> Global therapeutic approach

Tranexamic acid and melasma

- Double blind placebo control study in 44 patients
- Tranexamic acid 250mg X2/d + sunscreen for 3 months
- VS placebo + sunscreen for 3 months
- 3 additional months with sunscreen alone
- 39 patients completed the study
- A 3 months:
  - Decrease in mMASI of 49% with TA Vs 18% with placebo (p>0.001)
- No serious side effect. One subject dropped out for myalgia in TA group

*J Am Acad Dermatol. 2018;78:363-369*
Melasma

Photoprotection +++
(including against shorter wavelengths of visible light)
Discuss discontinuation of hormonal treatment +/-
Avoid friction

Kligman Trio for 3-4 months

Peeling (risk of PIH)
1550nm fr laser (risk of PIH)
1924nm thulium fr laser (few data and risk of PIH)

IPL
Pulsed dye laser

Tranexamic acid

Topical EDNRB inhibitors
DKK1 agonists
Chemical approaches to prevent visible light-induced pigmentation

Failure

Success

HQ 5%
Tretinoin 0.1%
Dexamethasone acetate 0.1%

Maintenance treatment:
Photoprotection++
Cosmetic blanching cream

Risk of PIH in skin types IV and higher
Off label used
To be determined
Thank you for your attention!