Photoprotection Beyond UV Spectrum

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Disclosure

• **Investigator:**
  - Estée Lauder
  - Ferndale
  - Allergan
  - Incyte
Learning Objectives

Be able to:

• Understand principles of photoprotection beyond the UV spectrum
• Describe agents that have this property
Photoprotection

- Shade
- Clothing
- Hat
- Sunscreens
- Sunglasses
- ? Non-topical agents

Sunscreens: Photoaging and Skin Cancer

(Hughes, MCB.... Green, AC. Ann Intern Med 6/13; 158:781;
Green, A., Lancet 1999; 354:723.

• A 4.5 yr + 8 yr f/u study of 1621 residents of Nambour, Queensland, randomly assigned to daily SPF16 broad spectrum sunscreen group, vs. control
• Sunscreen group had decreased
  • SCC
  • BCC
  • Photoaging
  • Melanoma
Sunscreens and Melanoma

(Green, A., J Clin Oncol. 2011 Jan 20;29(3):257-63. Brisbane, Australia)

• 1992-1996: 1621 residents of Nambour, Queensland, randomly assigned to daily SPF16 broad spectrum sunscreen group + 30 mg beta-carotene daily, vs. control.

• 2006 (10 yrs later):
  – Melanoma: 11 in tx gr; 22 in control
  – Invasive melanoma: 3 in tx gr, 11 in control.

• Melanoma may be prevented by sunscreen use
Ground Level
Spectrum of Sunlight
Beyond UV: Visible Light and Infrared
Photoprotection Beyond UV

- UV filters in sunscreens: designed to absorb UVB and/or UVA, not visible light
- External agents that protect against visible light: has to be opaque
  - Clothing
  - Zn oxide paste
- Need to consider systemic agents
Glass sculpture by Dale Chihuly  (American. 1941- )
Royal Ontario Museum, Toronto.  Dec 2016
UVA1 vs Visible Light
(Mahmoud, BH, et al. J Invest Dermatol 8/10; 130:2092)

70 minutes of sun exposure

UVA1
20 J/cm²

UVA1: 340-400 nm

Immediate 1 week
UVA1 vs Visible Light
(Mahmoud, BH, et al. J Invest Dermatol 8/10; 130:2092)

70 minutes of sun exposure

UVA1
20 J/cm²

Visible light
320 J/cm²

Immediate

1 week
UVA, UVB, PUVA-induced Skin Changes

W. Gange (courtesy of N. Kollias)
Synergistic Effect of Visible Light and UVA1

(Kohli, I, …, Lim, HW, Hamzavi, I. BJD 2017. Sept 6. Epub)

• 10 subjects; SPT IV-VI
• VL 480 J/cm², in the presence or absent of UVA1 (340-400 nm; 0.05%)
Synergistic Effect of Visible Light and UVA1

(Kohli, I, ..., Lim, HW, Hamzavi, I. BJD 2017. Sept 6. Epub)

<table>
<thead>
<tr>
<th>Visit</th>
<th>VL+UVA1</th>
<th>Pure VL</th>
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<tbody>
<tr>
<td>IPD Day 0</td>
<td>![Image]</td>
<td>![Image]</td>
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<tr>
<td>PPD Day 1</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>DT Day 7</td>
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<td>![Image]</td>
</tr>
<tr>
<td>DT Day 14</td>
<td>![Image]</td>
<td>![Image]</td>
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</tbody>
</table>

Average IGA score for Pigmentation

Visit

0 1 2 3 4

VL+UVA1 Pure VL

* * *
Possible Clinical Implications

- Visible light may have a role on conditions aggravated by sun exposure such as PIH and melasma, esp. in dark-skinned individuals.
- Currently available organic (chemical) UV filters are not sufficient to protect the skin from the effect of visible light.
- Antioxidants may be beneficial
Antioxidants in Sunscreens
Sunlight & Reactive Oxygen Species

ROS is generated following exposure to:

- UV, especially UVA
- Visible light *(Liebel, F. JID 7/12; 132:1901)*
Antioxidants & Sunscreens

Sunscreen + antioxidants >> sunscreen alone in:

• Suppressing UV-induced pigmentation, depletion of Langerhans cells, induction of MMP9

• Suppressing infrared A induction of MMP1
Antioxidants in Sunscreens

• Beneficial, provided they are stabilized and biologically active
Nanoparticles in Sunscreens
Titanium Dioxide

Red: 100 nm;  
Green: 50 nm;  
Blue: 20 nm.

Wang, SQ. Semin Cutan Med Surg 2011; 30:210-213
Nanoparticles

TiO$_2$ and ZnO ($<100$ nm)

- *In vitro*: can induce free radical formation in the presence of UV → damage of viable cells.
Nanoparticles


• Current evidence:
  – Remain mostly on surface of skin
  – Lodge in hair follicles; 0.000014% of applied amount detected in dermis surrounding hair follicles

• However,
  – Nanoparticles are coated
  – Skin has antioxidant mechanism
  – No evidence of having any consequence on human health
Nanoparticles

• Not sufficient data on inflamed skin where epidermal barrier function has been compromised.
Non-topical forms of photoprotection
Polypodium leucotomos Extract
**Polypodium leucotomos Extract**


- Fern plant extract from Central America
- Antioxidative and anti-inflammatory properties
- Suppresses:
  - Clinical changes induced by UVB, PUVA
  - Development of PMLE
- Role in visible light photoprotection
PLE: Safety


• Pubmed search: 19 human and 6 basic science studies; over 40 years.
• Oral PLE: 120 mg to 1080 mg per day.
• No adverse effects were reported in laboratory studies.
• In humans, side effects (gastrointestinal complaints and pruritus) were mild to moderate. 16/1016 (2%)
• PLE: well tolerated with a negligible risk of side effects.
Acute Effects of *Polypodium leucotomos* Extract

(Kohli, I, ...Elmets, C, Lim, HW, Hamzavi, I. J Am Acad Dermatol. 2017 (July); 77:33)

- 22 subjects
- PLE, 240 mg 2 hr and 1 hr before UVB irradiation resulted in:
  - Decrease of UV erythema
Acute Effects of PLE (n=22 subjects) 
(Kohli, I, ...Elmets, C, Lim, HW, Hamzavi, I. J Am Acad Dermatol. 2017 (July); 77:33)

Assessment by Colorimeter

“Shift” of skin phototype

↓ 18% 
(p<0.05)

Assessement by Colorimeter
Acute Effects of *Polypodium leucotomos* Extract

(Kohli, I, …Elmets, C, Lim, HW, Hamzavi, I. J Am Acad Dermatol. 2017 (July; 77:33)

- 22 subjects
- PLE, 240 mg 2 hr and 1 hr before UVB irradiation resulted in:
  - Decrease of UV erythema
  - Inhibition of markers of DNA damage and apoptosis (sunburn cells, cyclobutane pyrimidine dimers), inflammation (COX-2), and proliferation (cyclin D1, Ki67, PCNA)
Polypodium leucotomos Extract (PLE) and Visible Light

(Kohli, I, ...Lim, HW, Hamzavi, I. In progress. 2017)

• **Preliminary** in vivo data indicate that PLE:
  – ↓ immediate pigment darkening (IPD)
  – ↓ persistent pigment darkening (PPD)
  – No effect on delayed tanning (DT)
• PLE may be beneficial to the protection of VL-induced pigmentary changes on the skin
Nicotinamide
Oral Nicotinamide

- Nicotinic acid, niacin = Vitamin B3
- Nicotinamide (= niacinamide) is the amide of vit B3

In vivo

Nicotinic acid

Nicotinamide
Oral Nicotinamide

Chen, AC,... Halliday, GM. Photodermatol Photoimmunol Photomed 4-6/14; 30:102. Sydney)

• UV inhibits ATP production → energy crisis → prevents optimal skin immune response and DNA repair

• Oral nicotinamide (500 mg bid):
  – Blocks the inhibitory effect of UV on ATP production
  – Minimizes UV-immunosuppression
  – Enhances DNA repair
  – Unlike niacin, does not produce flushing reaction (niacin: lower lipid levels)
A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention

Oral Nicotinamide


- Phase 3 trial (= confirms effectiveness, monitor safety)
- Double-blind, randomized, controlled trial
- 386 participants with hx of NMSCs, randomly assigned (1:1):
  - Nicotinamide 500 mg bid
  - Placebo
- No differences in side effects
Oral Nicotinamide


Figure 3. Change from Baseline to Month 12 in Number of Actinic Keratoses.

Actinic keratoses
# Oral Nicotinamide


<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo mean no. of lesions/person</th>
<th>Nicotinamide</th>
<th>Rate Ratio (95% CI)</th>
<th>Relative Difference, % (95% CI)</th>
<th>P Value</th>
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<tbody>
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<td><strong>12-mo intervention period</strong></td>
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<tr>
<td>NMSCs</td>
<td>2.4</td>
<td>1.8</td>
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<td>23 (4 to 38)</td>
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<td>BCCs</td>
<td>1.7</td>
<td>1.3</td>
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<td>20 (−6 to 39)</td>
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<tr>
<td>SCCs</td>
<td>0.7</td>
<td>0.5</td>
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<td>30 (0 to 51)</td>
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<td><strong>6-mo postintervention period</strong></td>
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<tr>
<td>NMSCs</td>
<td>0.8</td>
<td>0.8</td>
<td></td>
<td>−17 (−59 to 14)</td>
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<tr>
<td>BCCs</td>
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<td>0.5</td>
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<td>−6 (−53 to 26)</td>
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<tr>
<td>SCCs</td>
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<td>0.3</td>
<td></td>
<td>−59 (−163 to 4)</td>
<td>0.07</td>
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</table>
Afamelanotide
Erythropoietic Protoporphyria
Solar Urticaria

Immediate: 24 hrs
Afamelanotide


• Potent analogue of human alpha-melanocyte stimulating hormone
• Bind to melanocortin 1 receptor (MC1R) → induces production of eumelanin, which is photoprotective
• Melanogenesis may provide a major antioxidant defense in melanocytes
α-Melanocyte Stimulating Hormone Analogues

Haylett, AF… Rhodes, LE. BJD 2/11; 164:407. Manchester, UK)

**EPP:**
- Afamelanotide, 20 mg s.c., twice, 60 days apart

**Solar urticaria:**
- Afamelanotide, 16 mg s.c., once

**Both:**
- Increased tolerance to artificial light
- Increased melanin content
Afamelanotide for Erythropoietic Protoporphyria

Afamelanotide for EPP: EU & US

- Randomized, double-blind, placebo-controlled study
- EU (74 pts): 5 subcutaneous implants, every 60 days
- US (94 pts): 3 implants
- Duration of pain-free time following sun exposure was longer in the treatment gr.
- Improved quality of life
- Adverse effects: headache, nausea, nasopharyngitis, and back pain
Non-topical Photoprotection

• Promising as an adjunctive photoprotective measure
• Not to replace current regimen of photoprotection
Learning Objectives

Be able to:

• Understand principles of photoprotection beyond the UV spectrum
• Describe agents that have this property
A Sunday on La Grande Jatte – 1884-86
Georges Seurat (French, 1859-1891). The Art Institute of Chicago