Diagnosis and Management of Actinic Keratosis (AKs)

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- **Faculty:** Andrei Metelitsa
- **Relationships with commercial interests:**
  - **Grants/Research Support:**
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Potential for conflict(s) of interest:

- [Andrei Metelitsa] has received [consulting payment] from [Leo Pharma Inc AND/OR Galderma Canada and Valeant Canada].
- [Supporting organization name] [developed/licenses/distributes/benefits from the sale of, etc.] a product that will be discussed in this program: [Picato, Metvix, Aldara].

Mitigating Potential Bias

- Dr. Metelitsa has worked with 3 companies that have currently approved medications in the treatment of actinic keratoses and is therefore able to present a balanced view on the treatment of this condition addressing all of the relevant therapeutics.

Objectives

- Benign Keratoses
- Actinic Keratosis
  - Clinical features
  - Local treatments
  - Field-directed treatments

Seborrheic Keratosis

Seborrheic Keratosis

- Common benign lesions that appear during the fourth decade of life
- Develop anywhere except mucous membranes, palms and soles
- Usually light brown but may appear brown-black in color
- “Stuck-on” appearance
- With trauma, the lesion may spontaneously “fall off”
- Cosmetic treatment: cryotherapy, electrodessication or laser

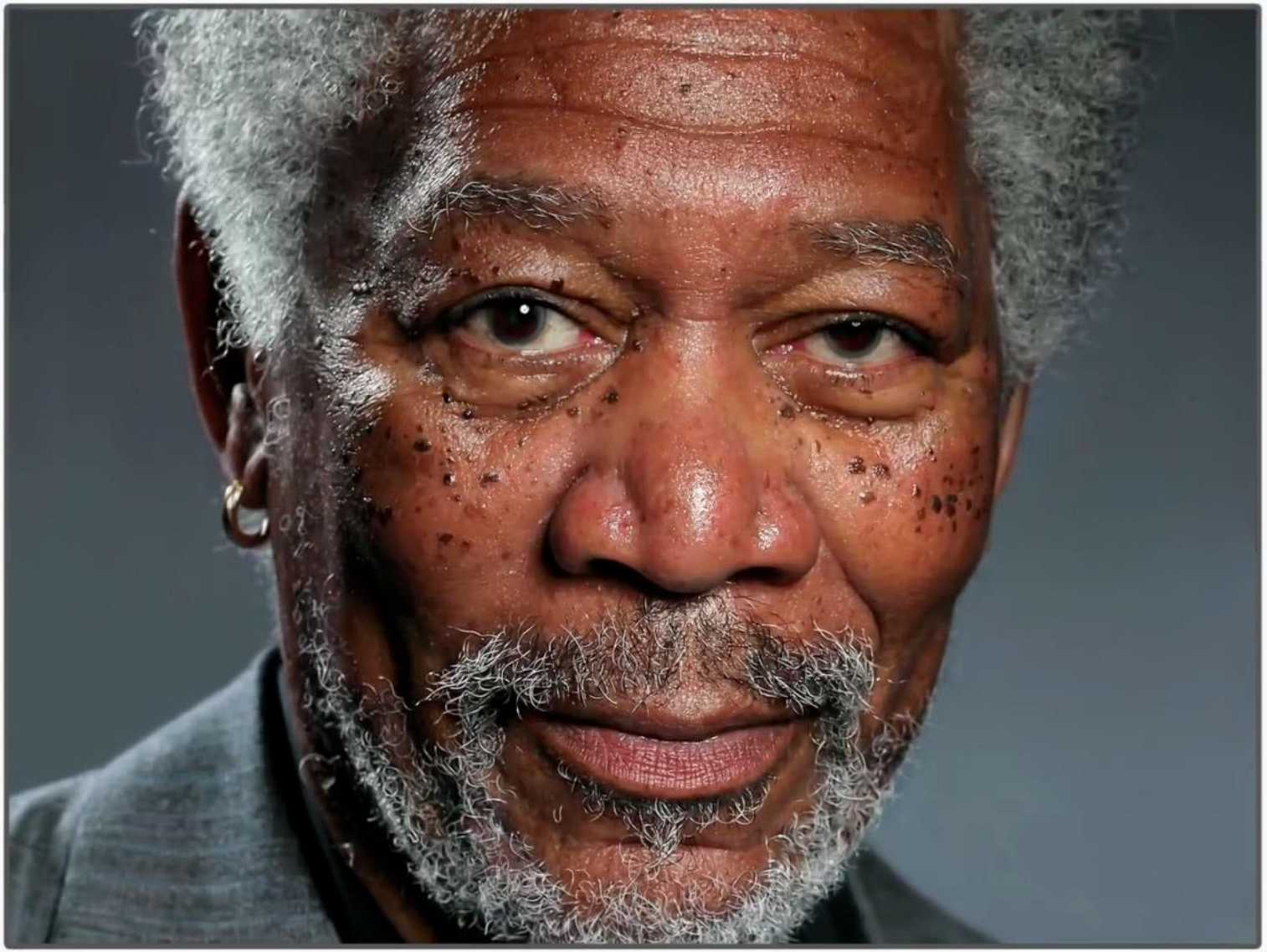
Stucco Keratosis

Stucco Keratosis

- Older adults
- Gray white papules usually on lower extremities
  - Favour ankles and dorsal feet
- Considered a variant of seborrheic keratosis
- Cosmetic treatment: cryotherapy, electrodessication or laser

Dermatosis Papulosis Nigra

Dermatosis Papulosis Nigra



Dermatosis Papulosis Nigra

- Most common in dark skinned individuals
- Multiple hyperpigmented papules on the face
- Considered to be a variant of seborrheic keratosis
- Cosmetic treatments
  - Electrodessication
  - Cryotherapy – risk of hypopigmentation

Actinic Keratosis

Actinic Keratosis

- Initially called solar keratoses
- Present on sun-damaged skin of the face, scalp, neck, and extremities
- Small 3-6mm red or brown scaly macules
  - Advanced lesions are thicker and well defined
- Detected by palpation due to their rough texture
- Clinical Diagnosis
  - Histology shows dysplastic keratinocytes and irregular nuclei
- Distribution: solitary, clustered, or disseminated

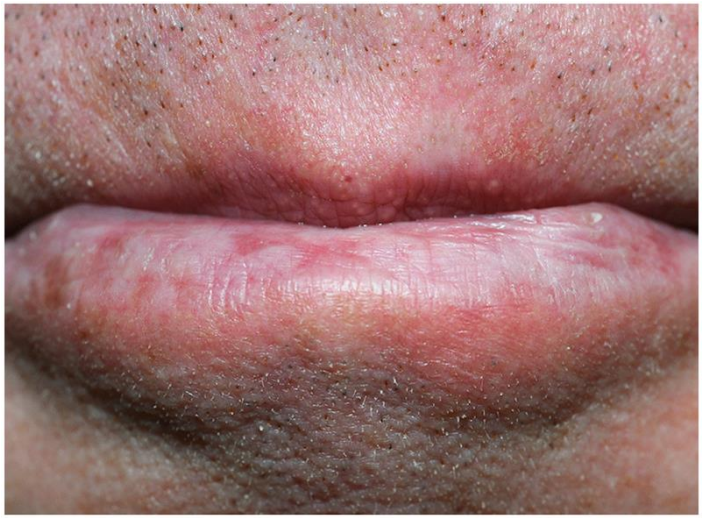
Risk Factors for Actinic Keratoses

- Fair skin (Fitzpatrick 1 and II)
- Significant cumulative sun exposure
- Prior history of AKs
- Prior history of skin cancers
- Increasing age
- Immunosuppression
- Prior use of tanning beds

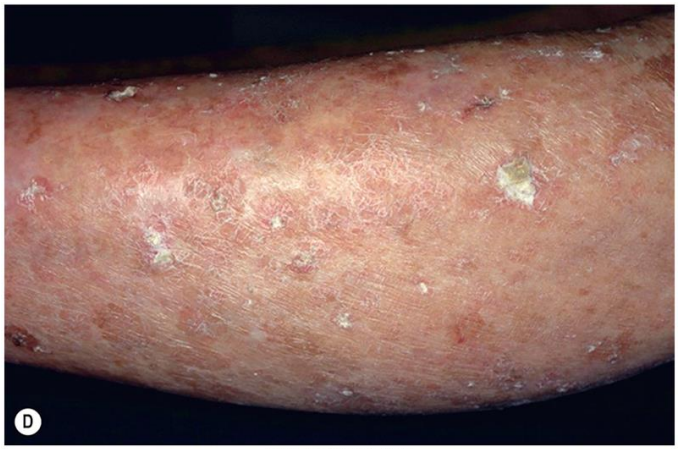
Management of Actinic Keratoses

- 3 pathways
  - Self-resolve
  - Persist
  - Evolve to Squamous Cell Carcinoma
    - Up to 1% progression per year (10% over 10 years)
    - Up to 80% of SCCs arise from AKs
    - Rapid enlargement, inflammation, large size, erythema and induration
    - AK lesions and SCC are frequently contiguous as they share the same genetic alterations and morphology

AK: Subtypes



Courtesy, Kalman Watsky, MD.



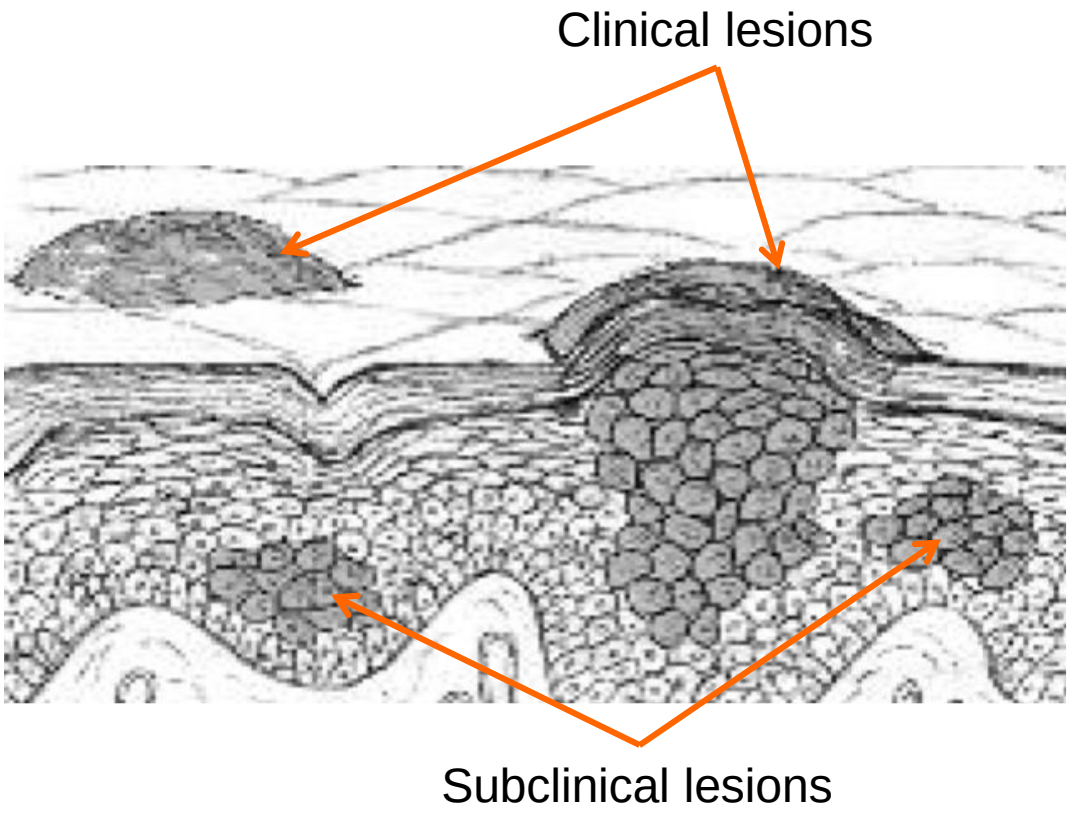
Courtesy, Jean L Bolognia, MD.

AK: Subtypes

- Diffuse photodamage
  - Clinical AKs
  - Subclinical AKs

Actinic Keratosis Is a Field Disease

- Field of cancerisation surrounds clinical AK lesions and is partially or completely clinically invisible – multifocal, paraneoplastic, subclinical changes
- Histopathology of AKs is found in surrounding skin
- Subclinical (non-palpable, non-visible) AK lesions occur ~10 times more often than clinical AK lesions in sun-damaged skin



Treatment Options for Actinic Keratoses

- Lesion-directed
  - Cryotherapy
  - Curettage/EDC
- Field-directed
  - Imiquimod
  - Ingenol mebutate
  - 5-flurouracil
  - Photodynamic therapy
- Combination

Field-directed Topical Treatment Options

Treatment	Therapeutic Class	Dosing	Duration of treatment
5-fluorouracil (5-FU)	Topical antineoplastic	Twice daily	Usual duration: 2-4 weeks
Fluorouracil/ salicylic acid (0.5%/10%) (Actikerall)	Topical antineoplastic	1x/day	Until completely cleared up to max 12 of weeks
Imiquimod 3.75% (Zyclara)	Immune-response modifier	Up to 2 packets once daily	6 weeks (2 treatment cycles of 2 weeks, separated by a 2-week no-treatment period)
Imiquimod 5% (Aldara)	Immune-response modifier	Twice weekly	16 weeks
Ingenol mebutate 0.015% (Picato)	Topical chemotherapeutic	Once daily	3 consecutive days
Ingenol mebutate 0.05% (Picato)	Topical chemotherapeutic	Once daily	2 consecutive days
Aminolevulinic acid (Levulan) or methyl aminolevulinate (Metvix) with PDT	Phototherapy with photosensitizer	Agents applied a day or a few hours before light treatment	1 to 2 treatment cycles May be retreated 8+ weeks or 3+ months[6] after initial treatment

Destructive therapies

- Cryotherapy
- Surgical excision
- PDT
- Laser resurfacing
- Chemical peels

Cryotherapy

- Most common approach to management of isolated AKs
- Preferred and most commonly used cryogen is liquid nitrogen due to its low boiling point (-196^{0}C) Standard treatment for actinic keratoses
- Advantage of being fast, low-cost procedure
- No cutting or anesthesia necessary
- Operator dependent (variations in freezing time and technique)
  - Cryopeeling used a field therapy in UK, but weak support in Canadian guidelines
- Complications
  - Risk of scarring and postinflammatory hypopigmentation (especially darker skin)
  - Pain, erythema and blister formation

Surgical Excision

- Solitary Aks are not typically excised
- Recommended in cases of diagnostic uncertainty or lesions refractory to treatment
  - Rule out invasive SCC
- Curretage recommended for hypertrophic Aks to debride lesions prior to applying other therapy
- Guidelines suggest use as a diagnostic tool

Photodynamic Therapy (PDT)

- Recommended for treatment of superficial and diffuse or located at sites of poor healing.
- For thicker AKs, more sessions of PDT may need to be given or AKs are pretreated with curettage to remove hyperkeratotic tissue before treatment
- 2 agents: aminolevulinic acid (Levulan) with blue light and methyl-aminolevulinate (Metvix) with red light.
- Patient response rates for around 2 cycles of PDT on face and scalp AKs ranged from 59.2% to 82%, with a 3-month follow-up.
- The cosmetic outcome of PDT was also rated higher than for cryotherapy.
- Currently, PDT is recommended as the first- line treatment for patients with multiple AKs, according to an international consensus

- **Adverse effects:** local pain, erythema, edema, crusting, photosensitivity
  - Metvix is considered to be less painful

Laser Resurfacing

- Utilizes either carbon dioxide (CO2) or erbium:yttrium aluminum garnet (Er:YAG)
- CO2 laser is often preferred
  - less painful and allows for faster wound healing
- The Canadian and European guidelines suggest using laser resurfacing for areas of clustered AKs, with one application repeated several times.
- Canadian guidelines have also mentioned laser resurfacing as an option in organ transplant patients

Chemical Peels

- Evidence is considered weak or poorly controlled
- Access is limited
  - Need specialist with extensive expertise in this procedure
- Medium depth pels compared to 5-FU
  - Simiar efficacy after 32 months
  - Aks may reappear and long-term follow-up is needed

Field therapies – used for multiple AKs

- 5-FU
- Imiquimod
- Ingenol mebutate

Topical 5-Fluorouracil (Efudex)

- 5% 5-FU twice daily for up to 4 weeks
  - Frequncy of application restricted due to erosive nature
  - Stop if develop erosion, ulceration and necrosis
  - Off-label once daily over 2-4 weeks
- A systematic review of 13 RCTs (n = 864) examining the efficacy of 5-FU
  - An overall 80% reduction in lesion count 50% of patients complete clearance
- **Adverse effects :** pain, pruritus, hyperpigmentation, burning at application site

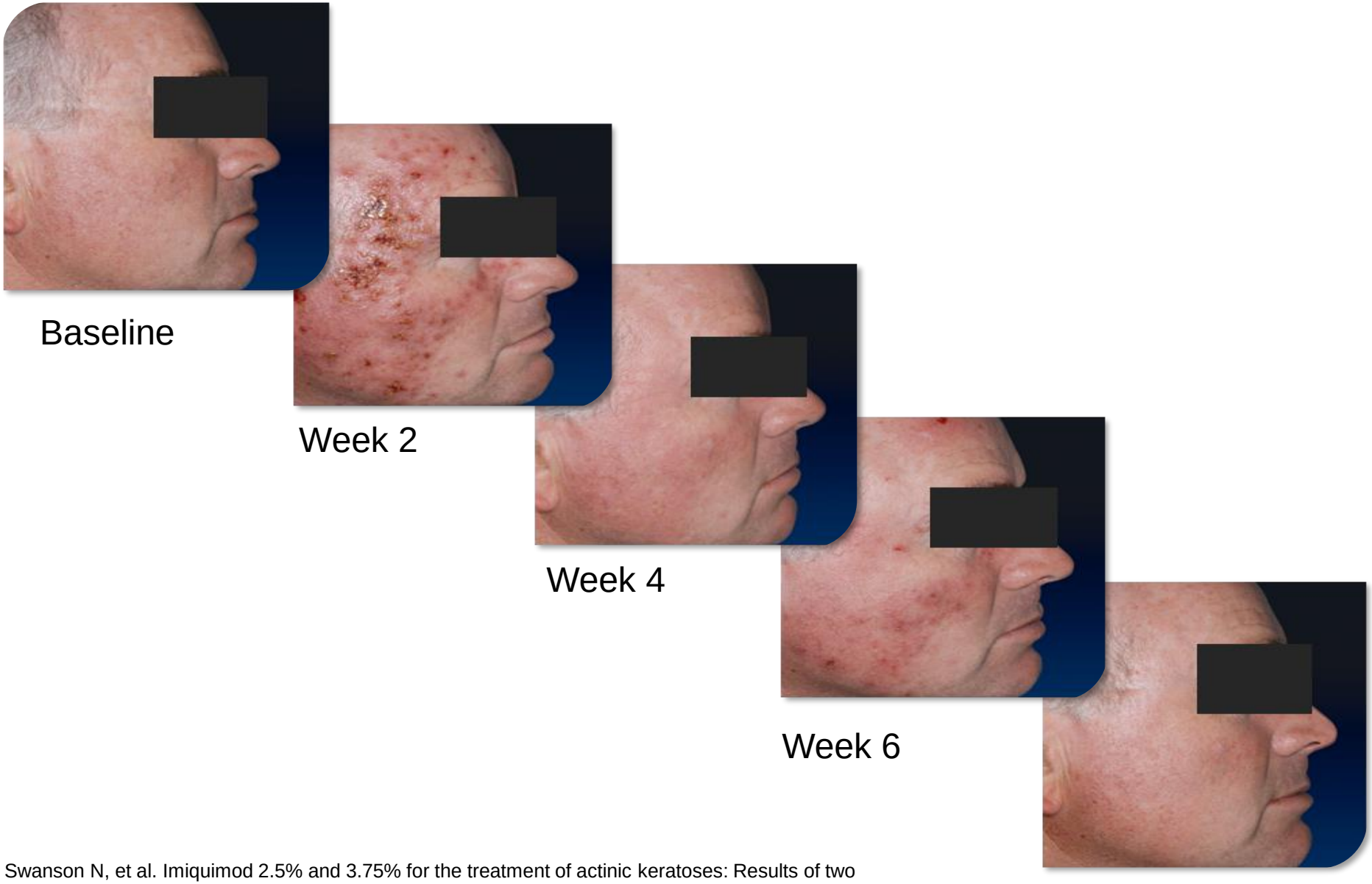
Imiquimod

- Induces cytokines and chemokines through Toll-like receptor-7 (TLR7) on dendritic cells (DC), Langerhans cells, macrophages and monocytes
- Enhances innate and cell-mediated immunity

- **5% (Aldara)**
  - **3x/week over 4 weeks**
  - Complete clearance rates from 26.8% to 57.1%
  - Partial clearance ranged from 36.6% to 72.1%

- **3.75% (Zyclara)**
  - **Daily over two 2-week cycles, 2 week rest period**
  - Complete clearance 34.0%
  - Partial clearance 53.7%

Moderate Reaction and Clearance



Swanson N, et al. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: Results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles. J Am Acad Dermatol 10.1016/j.jaad.2009.07004.

Ingenol Mebutate Gel (Picato)

- From the sap of *Euphorbia peplus*
- Rapid and direct cell death, disruption of mitochondrial membranes, activation of adhesion molecules and protein kinase C delta, recruitment of neutrophils
- Face and Scalp: 0.015% OD x 3 days
- Trunk and extremities: 0.05% OD x 2 days
- Up to 25 cm^2 contiguous Rx area

Ingenol Mebutate Gel (Picato)

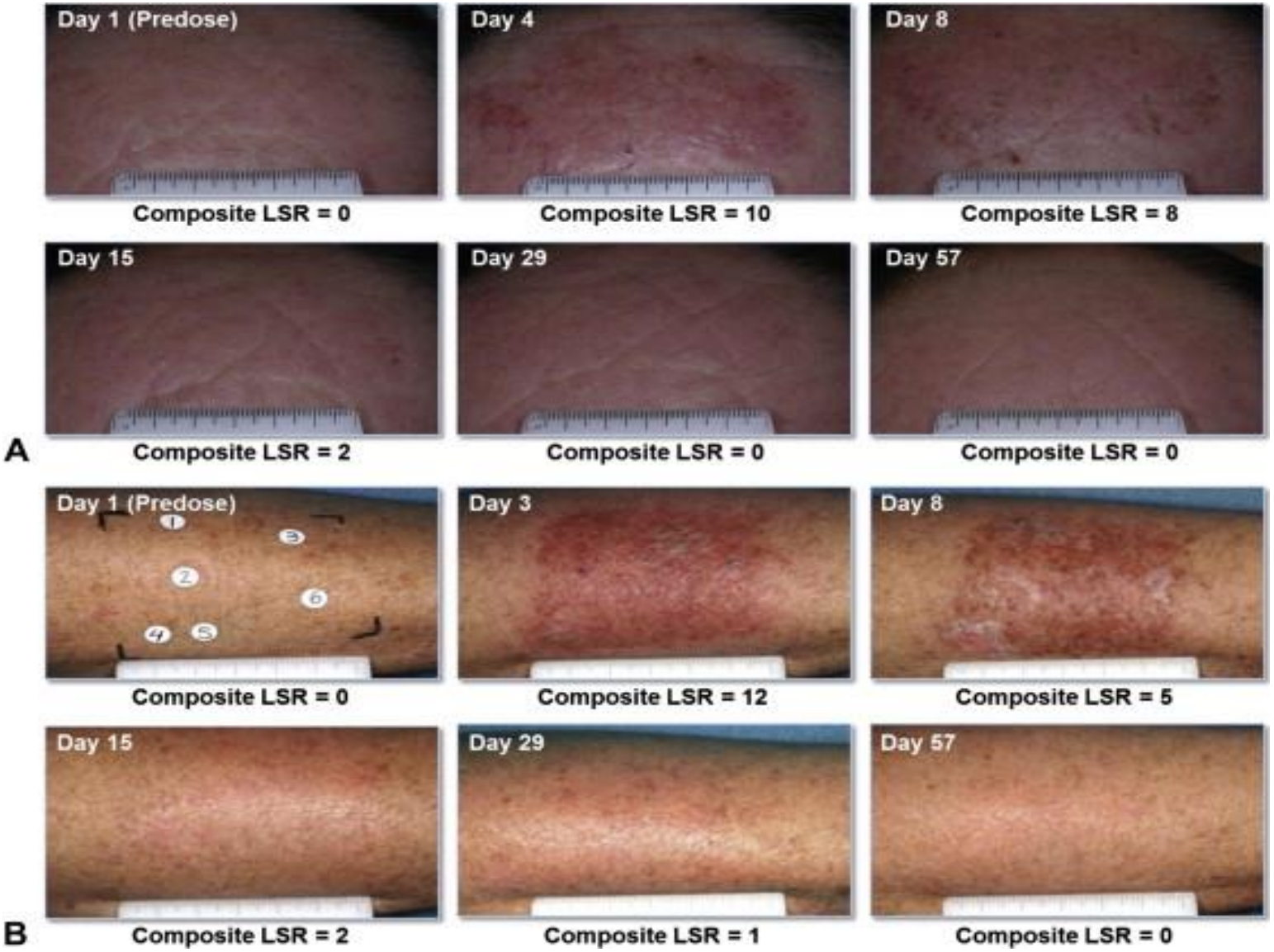
- Active agent in the sap of the plant *Euphorbia peplus,* which has long been used as a traditional remedy for common skin lesions, including cancerous lesions.
- Induces rapid and direct cell death and immune responses mediated by specific activation of protein kinase C delta, including neutrophil-mediated oxidative burst and clearance of tumors.

- Face and Scalp: 0.015% daily x 3 days
- Trunk and extremities: 0.05% daily x 2 days
- Up to 25 cm^2 contiguous Rx area

Ingenol Mebutate Gel Efficacy

- Partial clearance 49.1% to 75.4%
- Complete clearance 42.2 % to 71%
- Short treatment interval is beneficial for patients vs. imiquimod and 5-FU
- Has been used after cryosurgery with higher clearance rates

Ingenol Mebutate Gel for AKs



Comparative Table of AK Treatment

Treatment	Complete clearance, % patients	Follow-up period	Patients with sustained clearance, %	Follow-up period
Cryotherapy	68–76%	3 months		
5-FU	48–58%	4 weeks	54%	12 months
Imiquimod 3.75%	36%	8 weeks	41%	12 months
Imiquimod 5%	45%	8 weeks	43%	12-18 months
Ingenol mebutate 0.015%	42%	2 months	46%	12 months
Ingenol mebutate 0.05%	34%	2 months	50%	12 months
Photodynamic therapy (PDT)	59–82%	1–3 months	40%	12 months

Conclusions

- Actinic Keratoses can progress into SCC
  - Early detection and management
  - Sunprotection education
- When dealing with multiple lesions, consider field therapy
  - Treatment of subclinical lesions