A Split Face Evaluation of a Novel Topical Oxygen Emulsion on the Healing Process Following Photodynamic Therapy: A Pilot Study

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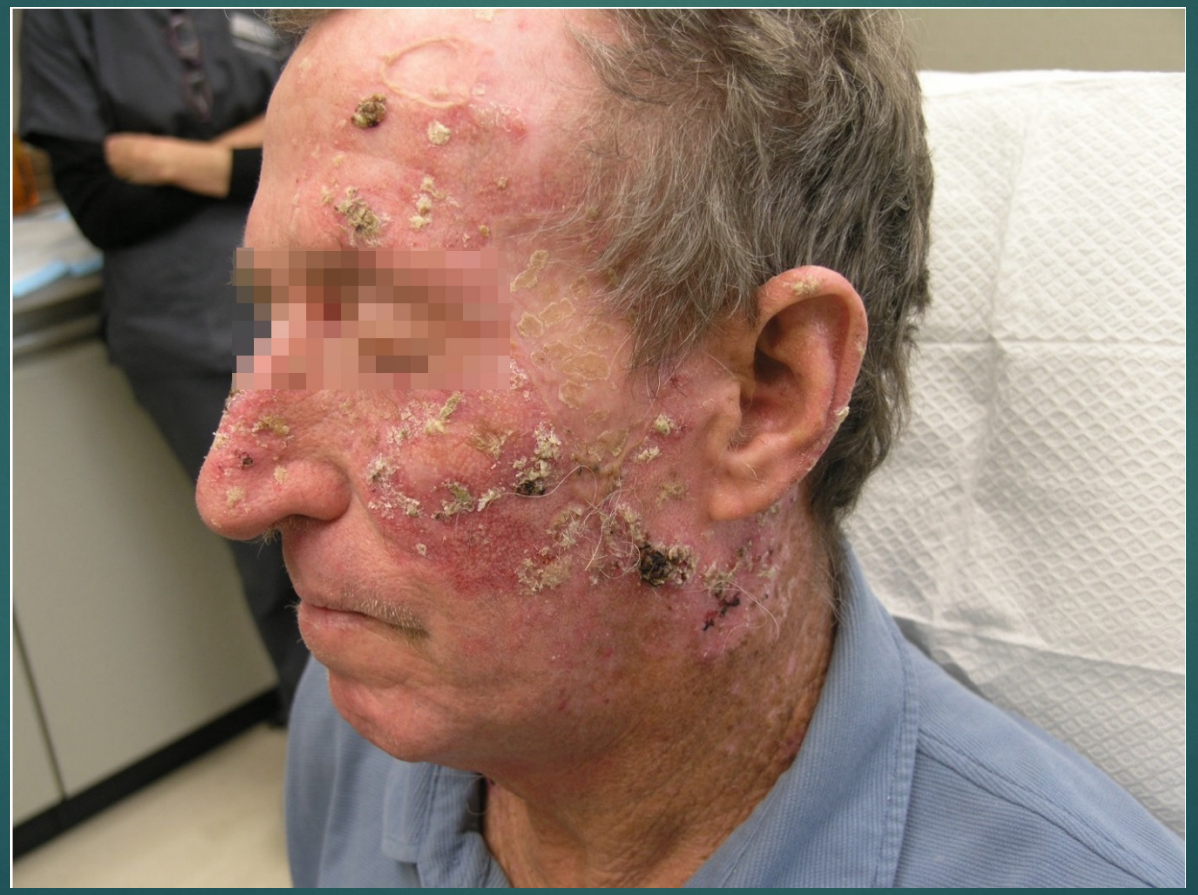
Introduction

- PDT – established FDA approved modality for the treatment of actinic keratoses
- Additional areas of interest include acne, NMSC, inflammatory disorders, potential aesthetic benefit
- Beneficial for patients with actinic damage, AKs, prior NMSC, SOT
- Useful for "field therapy"
- Prevention of precursor lesion of SCC- the actinic keratosis
- Protocols include two (2) treatments separated by 8 weeks
- Basics of PDT have been highlighted
- Sensitizer (ALA) is selectively taken up by hyperproliferative tissues

Candidate for PDT



PDT Morbidity Treatment

- Actual treatment under light source-

1. Burning
2. Stinging
3. Pain

- Patient's treatment tolerance varies substantially

PDT Morbidity Post Treatment

1. Photosensitivity
2. Edema
3. Erythema
4. Vesiculation
5. Pain
6. Anxiety, lost sleep
7. Time lost from work and routine activities

Unfortunately, some patients flatly refuse additional treatments following the initial treatment due to the above

The observation that patients experience significant post PDT morbidity is undeniable

Management of PDT Induced Clinical Side Effects

- PDT treatment – fans, chilled air, "Talkesthesia"
- Post PDT- ice packs, chilled gel packs, PO meds: NSAIDS, acetaminophen, narcotics; anxiolytics, sleep aids
- **REAL PROBLEM**

Purpose of our Study

- Can we reduce post PDT clinical morbidity of pain, edema, erythema, shorten healing time, and time lost from work and routine activities?

If so, the product needs to be:

- Safe
- Effective
- Easy
- Affordable

Split Face Evaluation of a Topical Oxygen Emulsion (TOE) on the Healing Process Following PDT- Pilot Protocol

- 10 patients; written informed consent; baseline photos and AK counts
- Treatment protocol:

1. Alcohol gel followed by acetone prep; topical ALA entire face- 120 minutes
2. Photoactivation with BLU-U light source for 16 minutes; Zimmer chiller
3. Post treatment written instructions: 48-hour UV avoidance
4. TOE applied to left face; Aquaphor to right face bid-tid; written log
5. Patients returned for photo documentation frequently

Pilot Protocol-II

6. Post treatment questionnaire:

- Evaluate product's effect on side effects: edema, erythema, stinging, pain
- Did one side heal faster?
- Would they request this for additional PDT treatments?

7. Patient pre and post treatment photos were compared for clinical post treatment side effects of erythema, edema, etc.

8. Efficacy of treatment based on lesion counts at 30 & 60 days

9. Follow up for 12-month evaluation

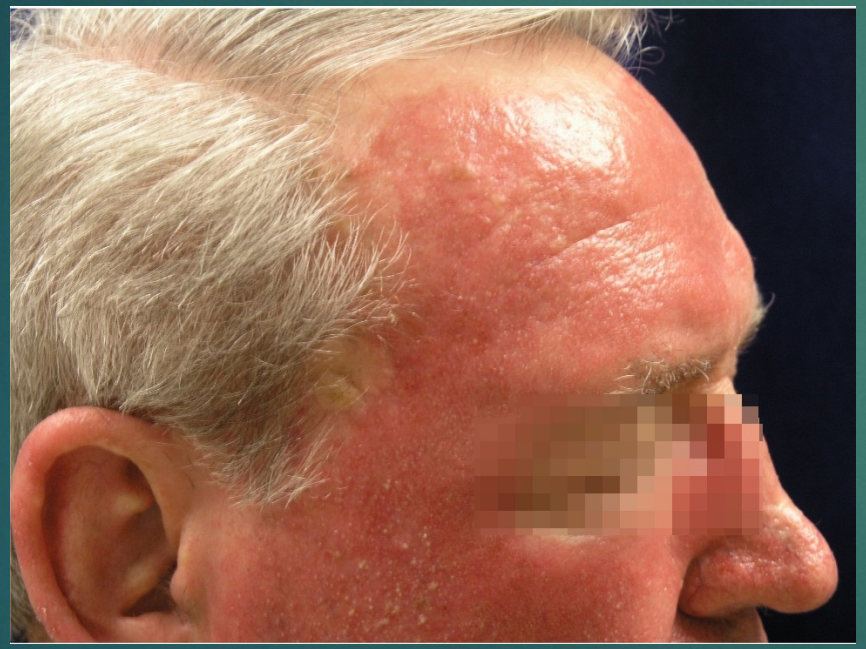
Results

- Patients: 9 male 1 female
- Age:52-76 Type II-III skin
- No adverse effects (e.g. contact dermatitis, irritation) due to TOE
- Post treatment photos demonstrated a sharp contrast on the TOE side (L) compared to the control- Aquaphor side (R) at 24 hours with reduced edema and erythema, and subsequent days of 1st week
- Speed of healing was more rapid on the left face in all patients
- All patients reported an almost immediate cessation of burning and stinging post initial application (within 10 minutes) on the treated side
- Treatment side (L) did not demonstrate any reduced efficacy of AK clearance based on comparison of lesion counts

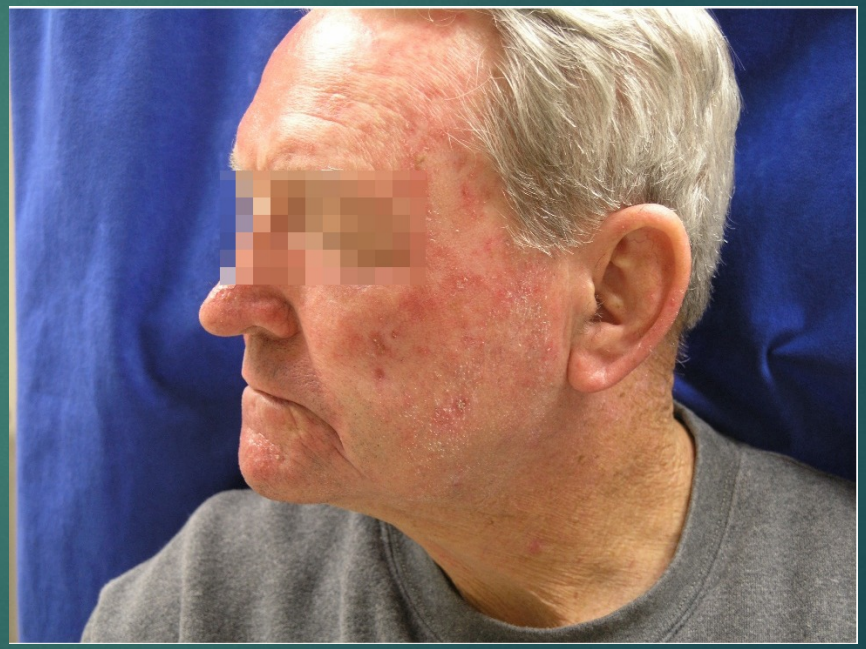
Patients in Study

Patient #1 Post op day #1

Right-Control

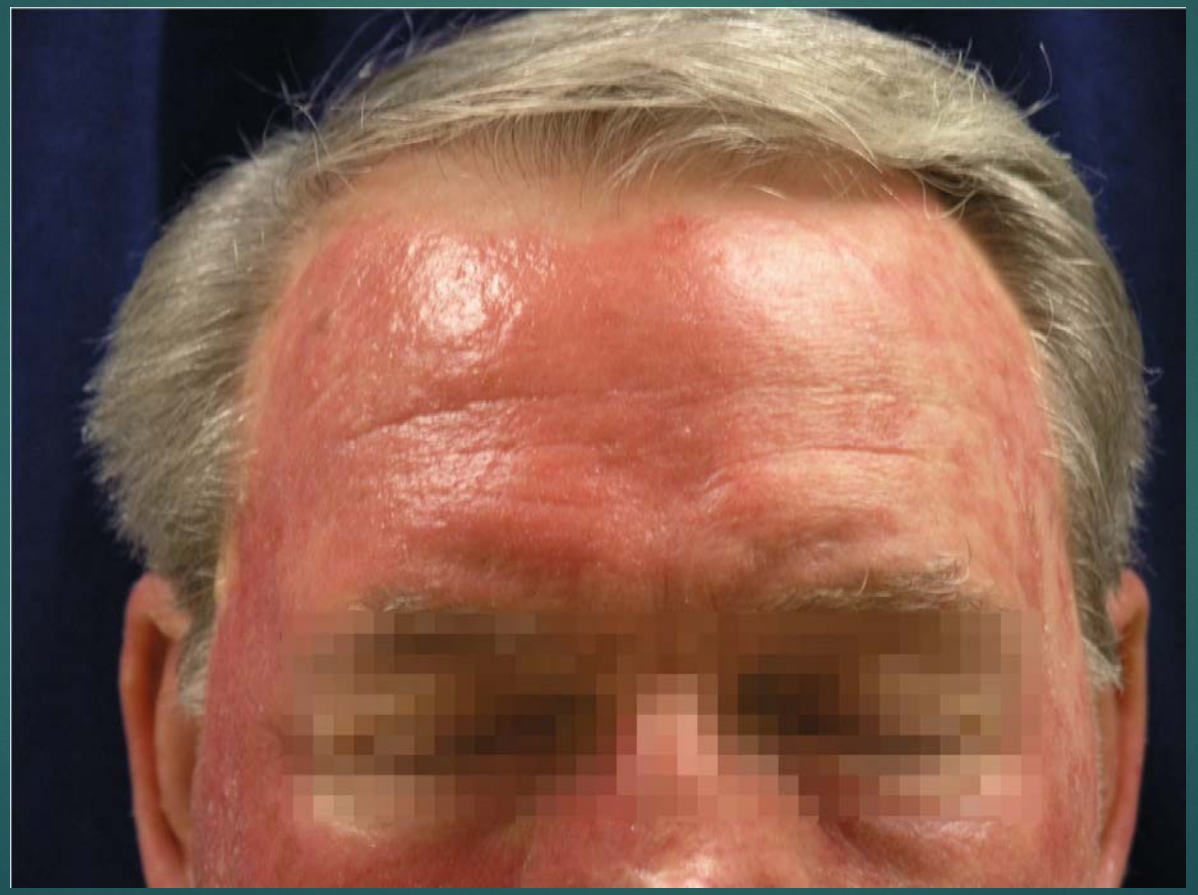


Left -TOE



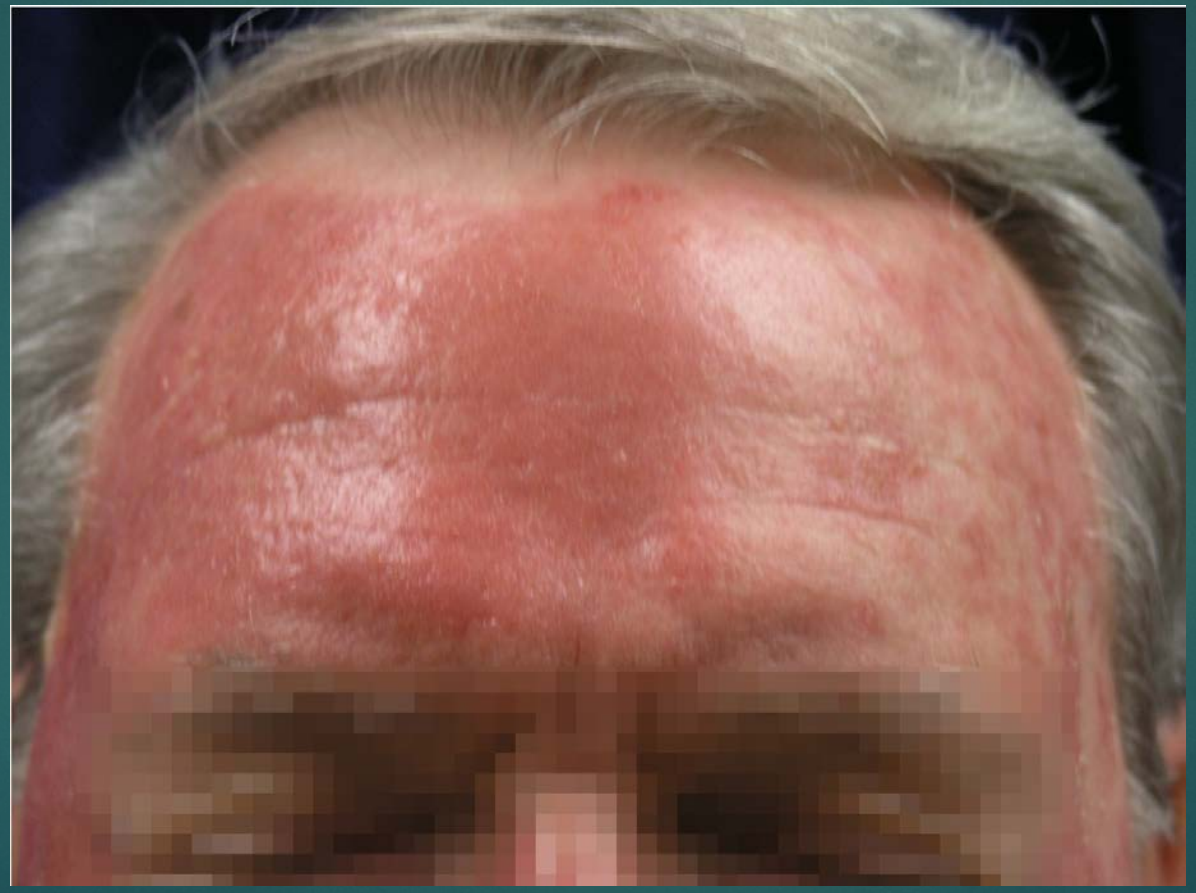
Patient #1 Post op day #1

Right-Control Left-TOE



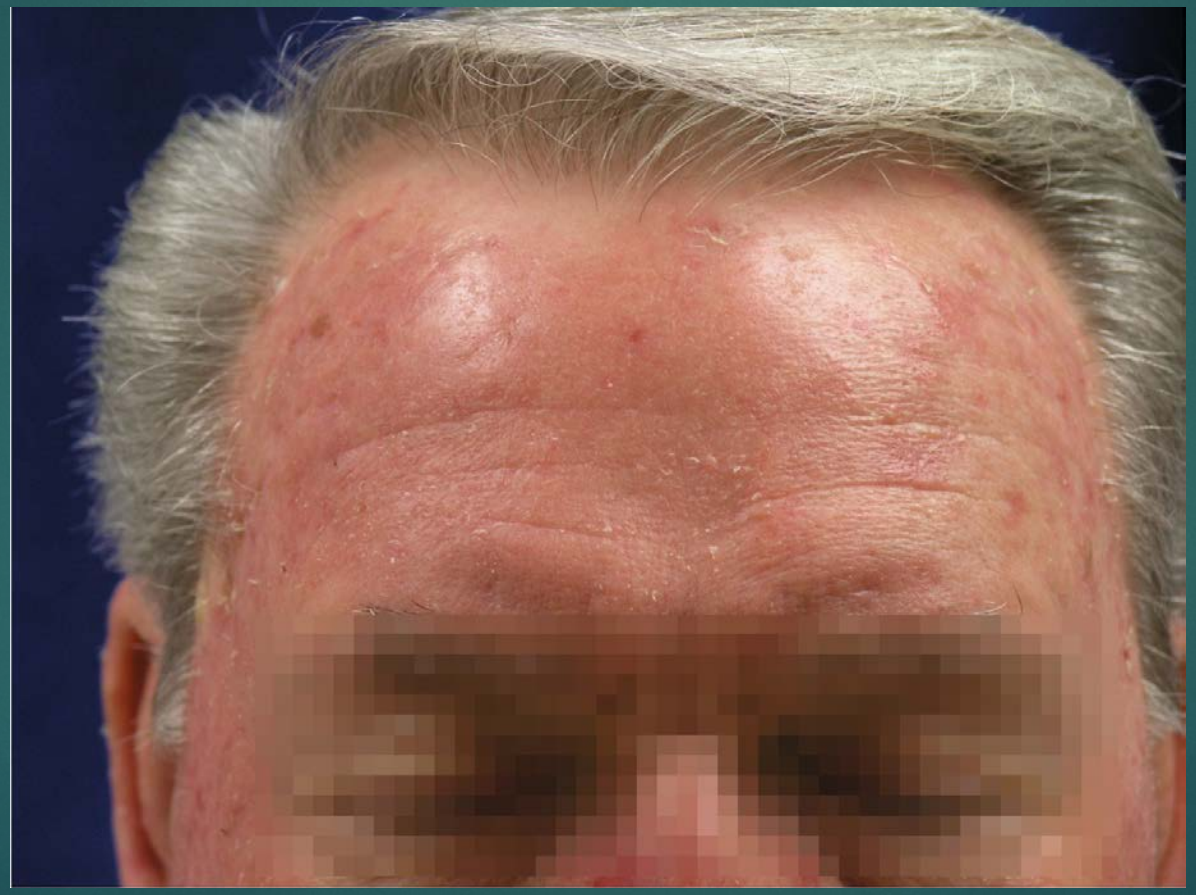
Patient #1 Post op day 1

Right- Control Left- TOE

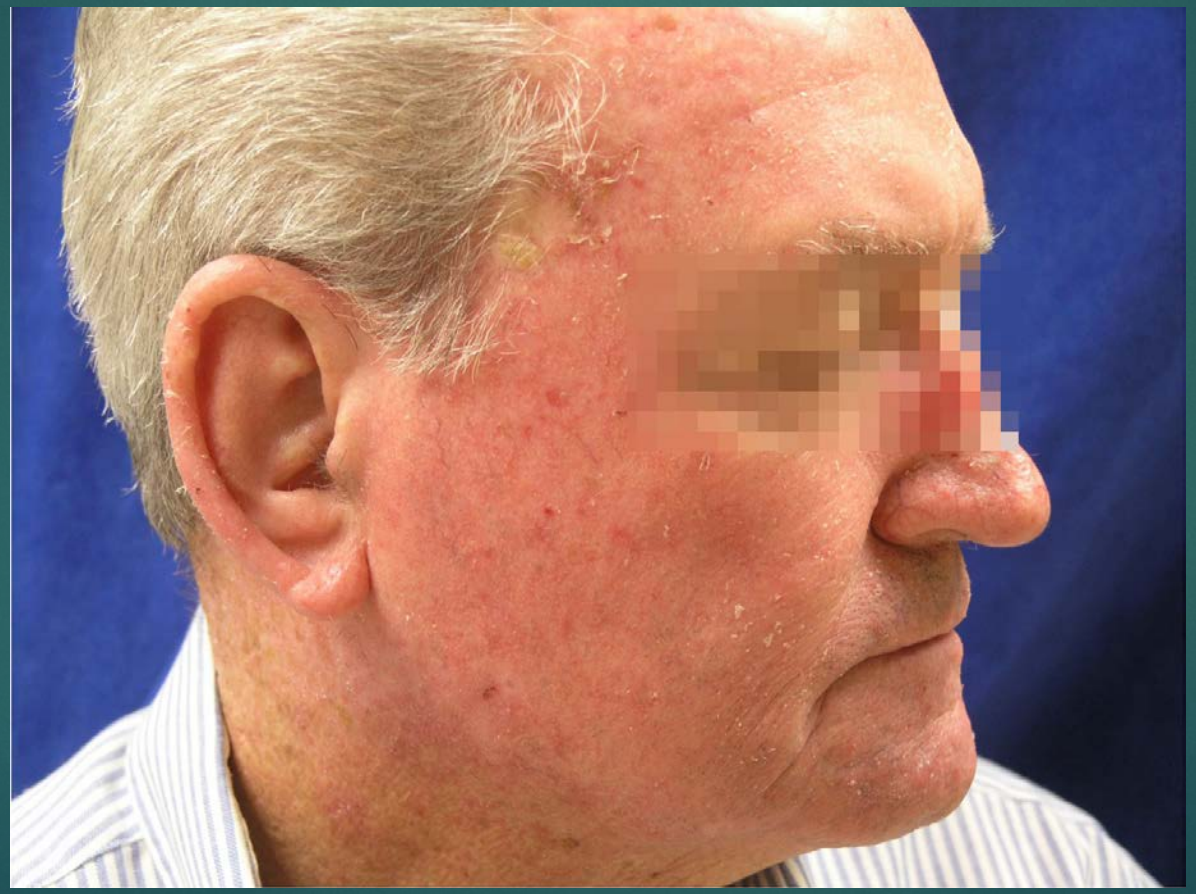


Patient #1 Post op day 5

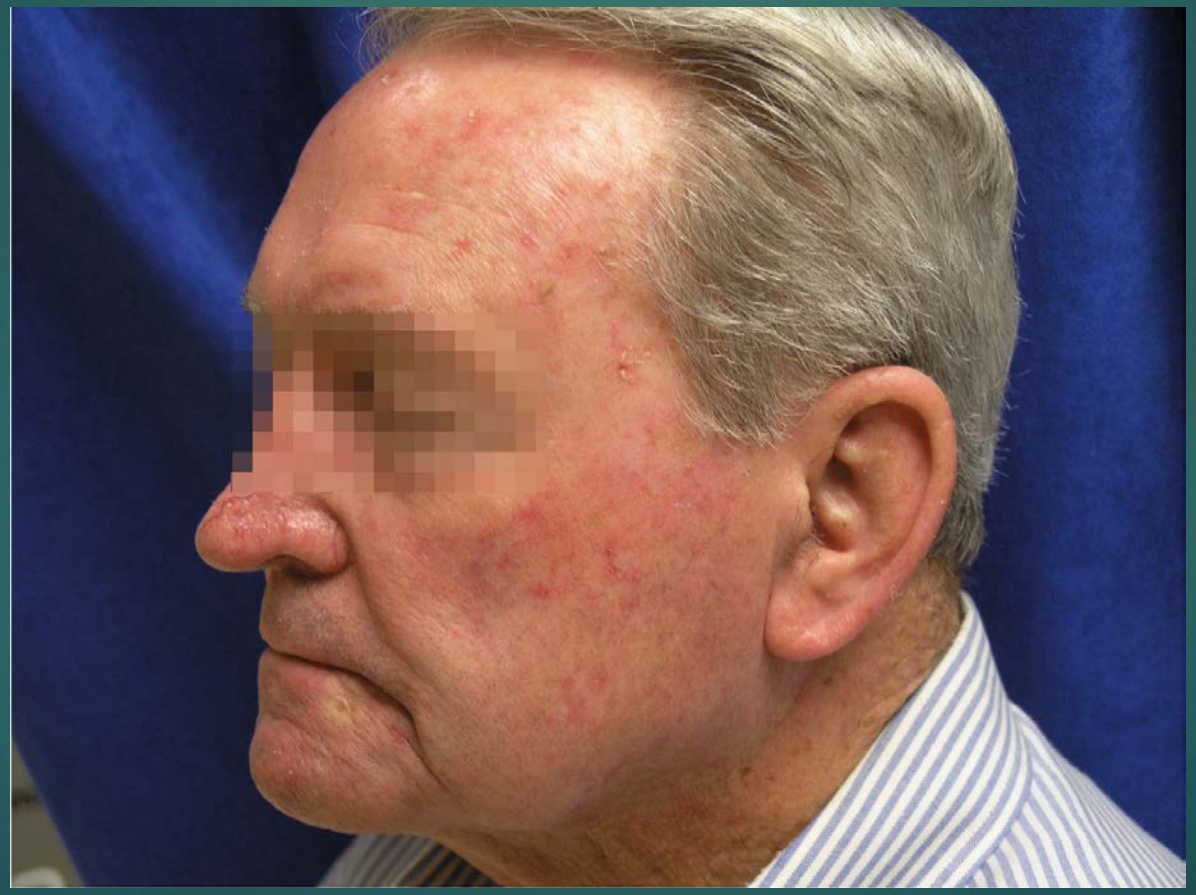
Right - Control Left - TOE



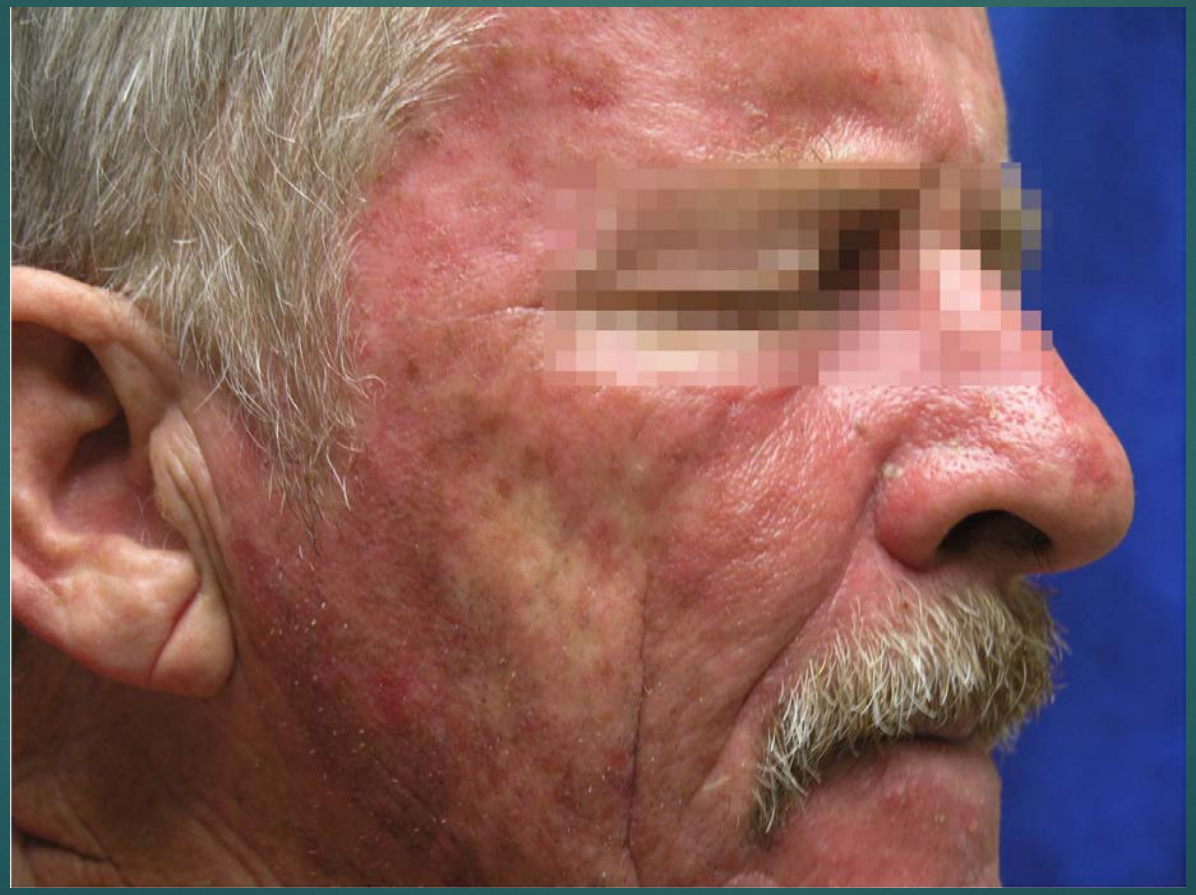
Patient #1 Post op day 5
Right - Control



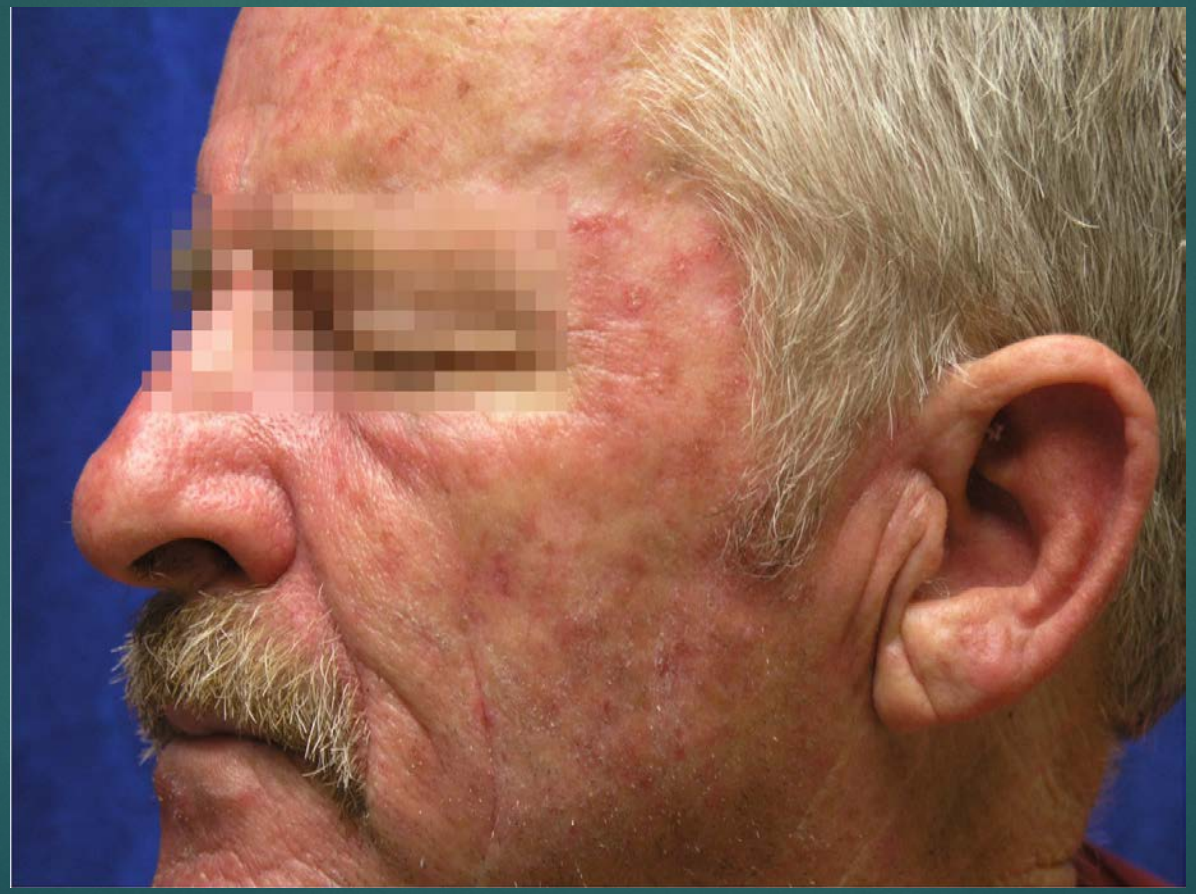
Patient #1 Post op day 5
Left - TOE



Patient #3 Post op Day #2
Right Side- Control

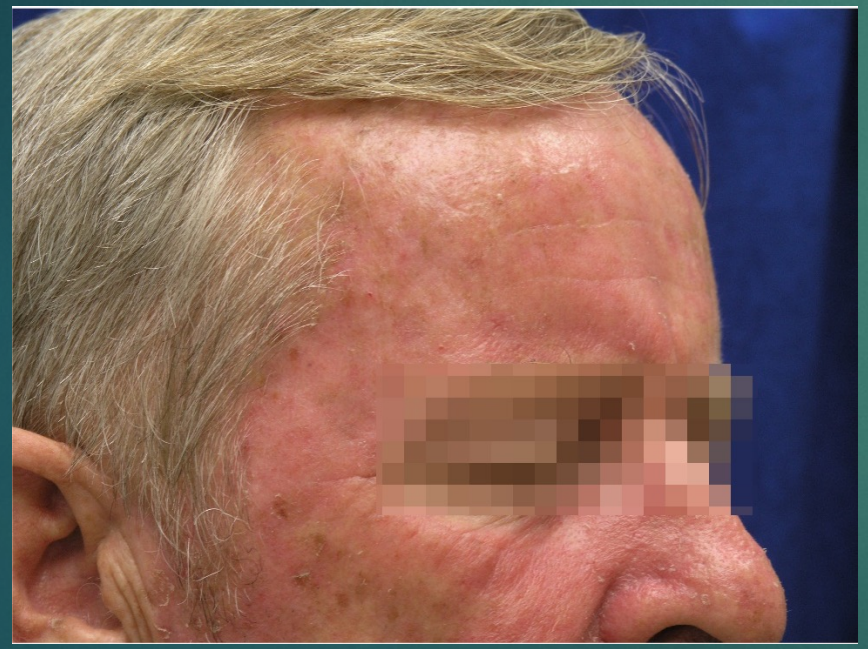


Patient #3 Post op Day #2
Left-TOE

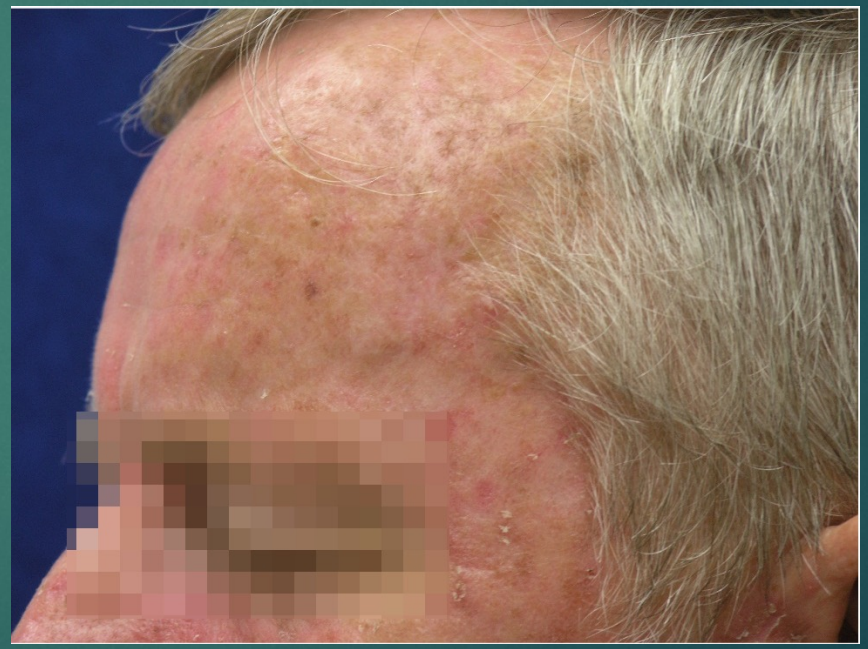


Patient #3 Post op Day #6

Right-Control

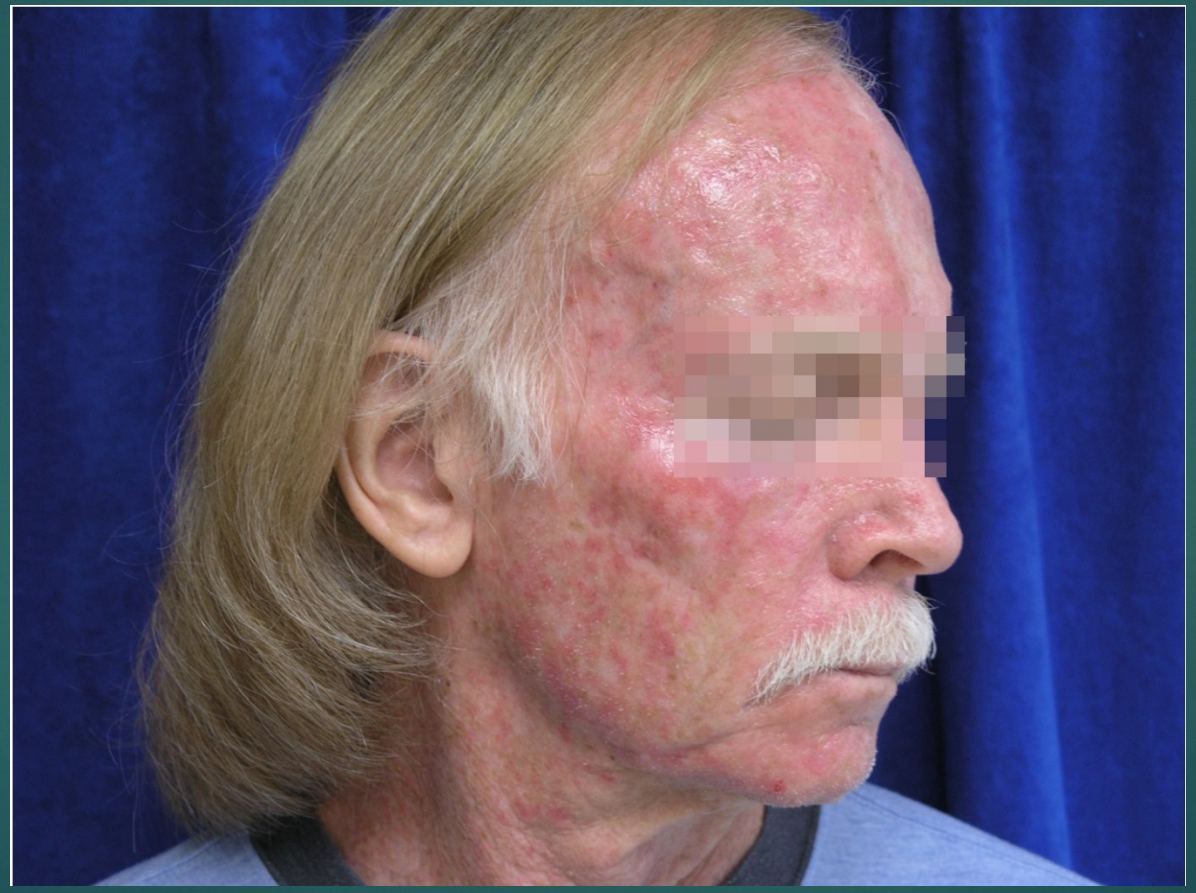


Left-TOE



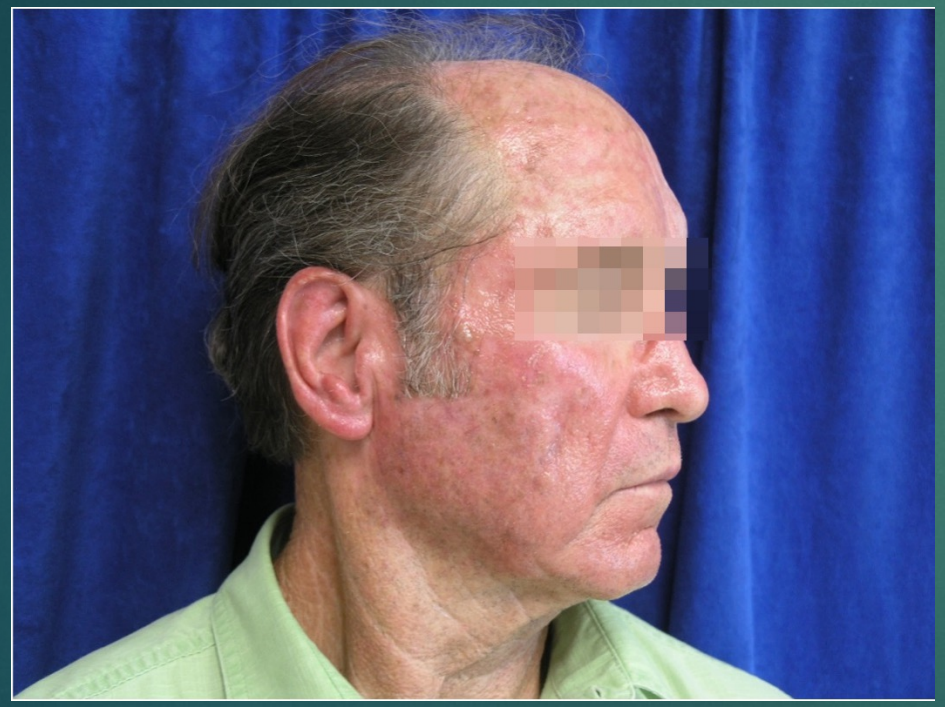
Patient #10 Post PDT Day 1

Right-Control Left -TOE

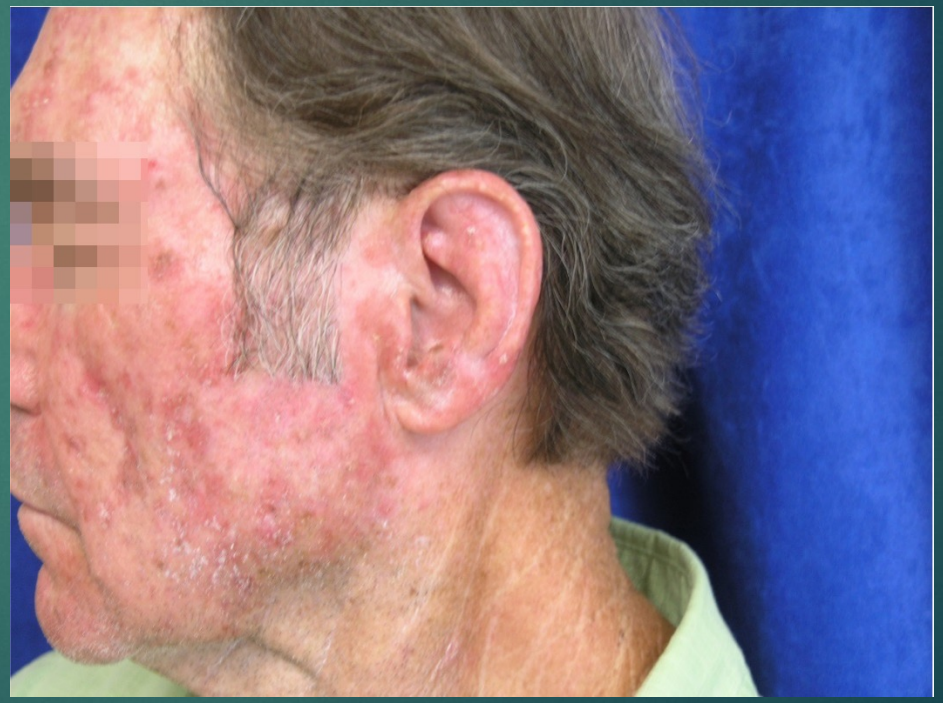


Patient #6 Post PDT Day #1

Right-Control



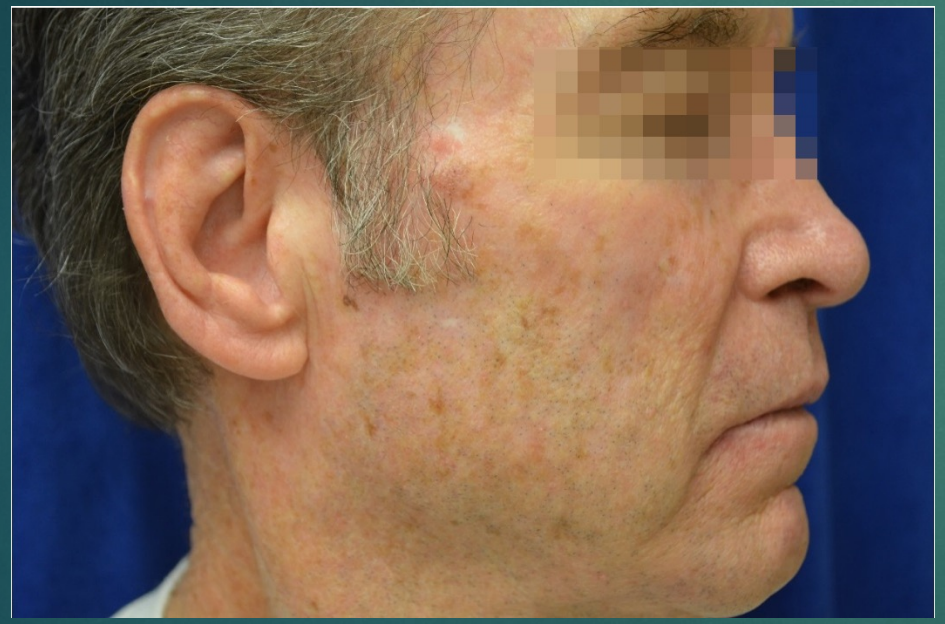
Left-TOE

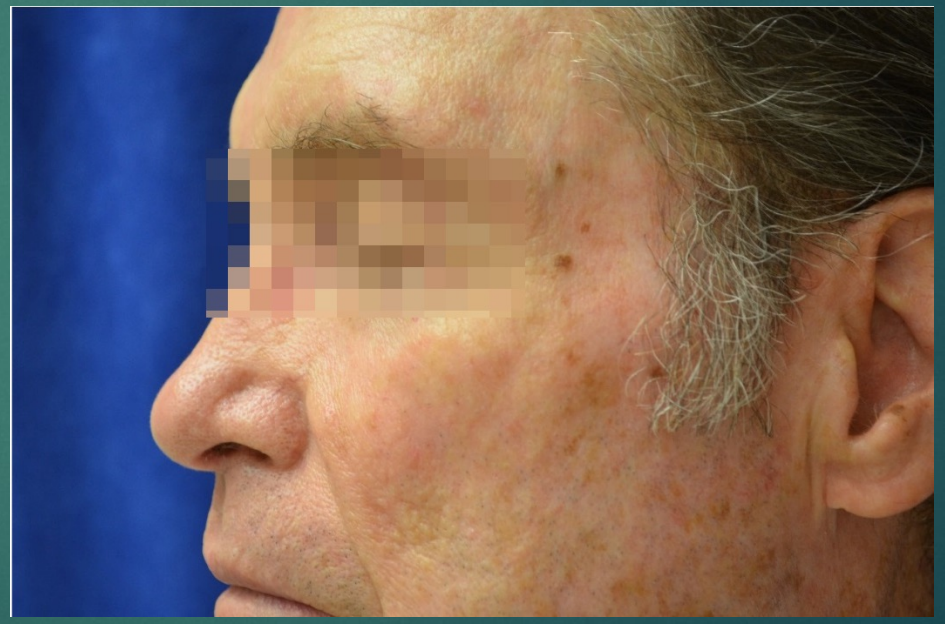


Patient # 6 12 Months Post PDT

Right- Control

Left- TOE





Discussion

- PDT is a proven modality to reduce AKs and actinic damage helpful- especially NMSC and SOT patients
- Our pilot study utilized a TOE product applied to the skin immediately following standard blue light PDT and through the 1st week post treatment
- 100% of our study group demonstrated clinical reduction of PDT induced pain, erythema, and edema; **and** more rapid healing on the treatment side
- Treatment efficacy was not reduced on treatment side compared to control

Discussion

- Mechanisms of action of PDT are many and include: generation of multiple ROS; phototoxic cellular injury, micro-vascular injury, apoptosis, immune response generation
- Following initial tissue injury, the above including micro-vascular injury triggers a cascade of hemostatic events with generation of various chemotactic cytokines (PDGF, VEGF); inflammatory cells…..
- Wound healing is a complex overlapping sequence of 3 well orchestrated phases well known to dermatologists

Discussion
Questions to consider

- What is a topical oxygen emulsion and how is produced?
- What does application of a TOE do to tissue O_2 tension-measurements?
- What caused the rapid clearing of our patient's post PDT side effects?
- Was the increased oxygen tension or vehicle responsible for our clinical observations?
- Something else?

What is a topical oxygen emulsion and how is produced?

- As a gas, O_2 has limited ability to penetrate the skin
- Production of an emulsion containing supersaturated oxygen can be delivered topically to skin which can slowly release additional oxygen over time.
- Technology is based on perfluorocarbon droplets being encapsulated within an aqueous phase generated when oxygen is placed under increased atmospheric pressures.
- O_2 saturation of perfluorocarbons is relatively high (approx. 20 times greater than H_2O)- high oxygen carrying capacity.
- Oxygen is dissolved into the perfluorocarbon emulsion under pressure into a dispensing container.
- Maintaining this under pressure prevents dissolution and outgassing during storage until dispensation
- The topical vehicle is formulated with biocompatible emulsifying agents to ensure stability

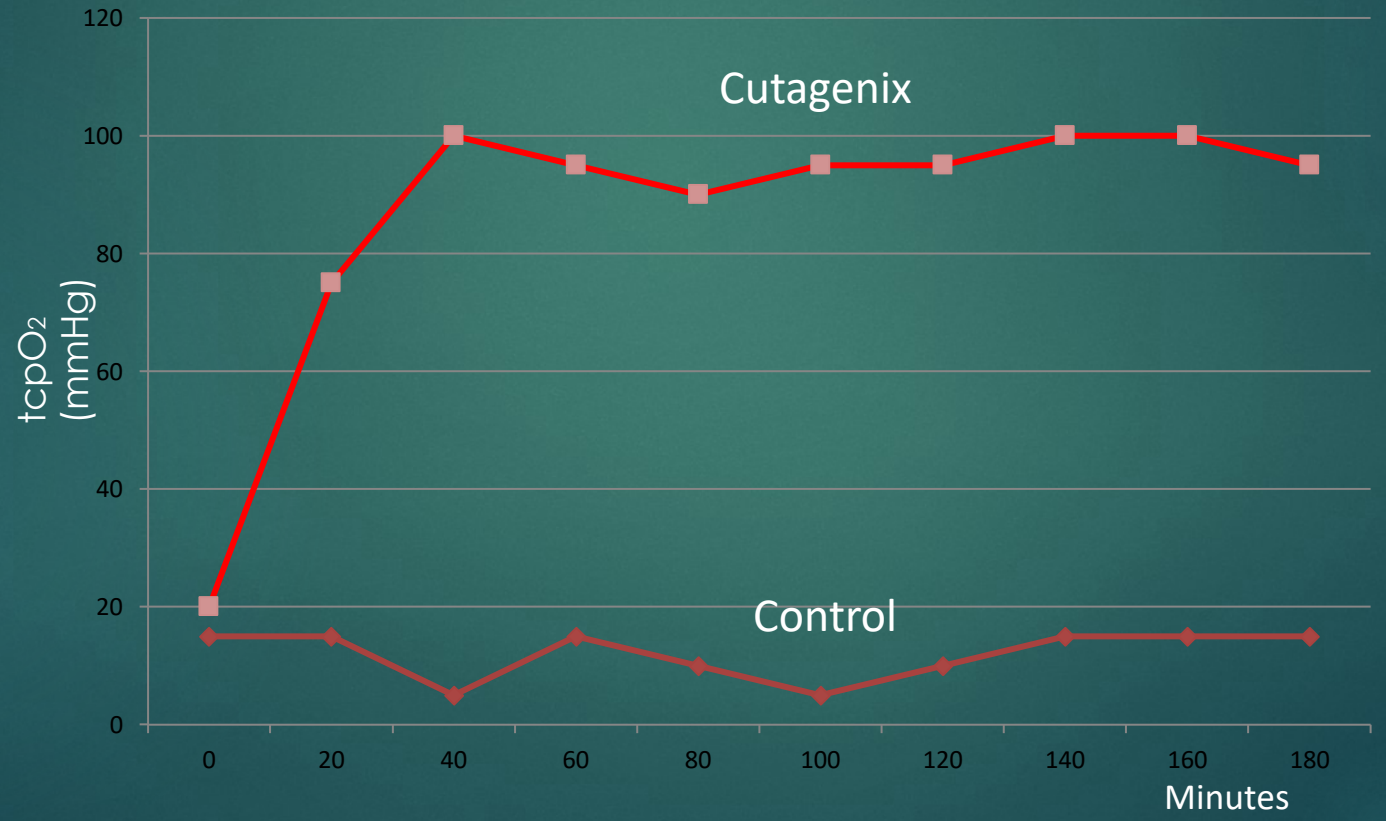
What a Topical Emulsion is Not

- Hyperbaric oxygen (HBO)- delivered in a sealed chamber with 100% O_2 at increased atmospheres (2-3)
- Topical HBO
- Any use of the term topical HBO is both misleading and a misnomer

What Does an Application of a TOE do to Tissue O_2 Tension- Measurements?

Skin $tcpO_2$ After Cutagenix Application

- Split face study wherein $tcpO_2$ was measured on the experimental and control sides 20 minutes after Cutagenix was applied using a Radiometer TCM40 monitor
  - ✓ Post-procedure (face lift) skin treated with Cutagenix showed $tcpO_2$ levels that were 3 to 5 times higher compared to the non-treated side (control)
  - ✓ Sustained $tcpO_2$ levels were maintained for 3 hours until measurements were stopped



What Caused the Rapid Clearing of our Patient's Post PDT Side Effects? Increased Oxygen Tension?

- Attractive hypothesis
- What does data show?
- Two studies –
- Draw backs- small size and only animal models up to this point

Davis, CD et al: TOE Study *Arch Dermatol*. 2007;143(10);1252-1256

- Double blind, control in-vitro study with pig skin
- Partial thickness wounds and 2nd burns were assessed for rates of epithelialization using a salt-split technique to separate the epidermis and dermis
- 3 Groups evaluated: TOE, vehicle, untreated air-exposed
- Partial thickness wounds- wounds receiving TOE had a significantly enhanced rate of epithelialization compared with the vehicle and untreated air-exposed wounds
- 2nd burn group showed similar enhanced rates of epithelialization compared to vehicle and untreated air-exposed wounds

Criticism: TOE can't deliver oxygen deep into skin to effect keratinocytes, inflammatory cells, and fibroblasts to effect wound repair.

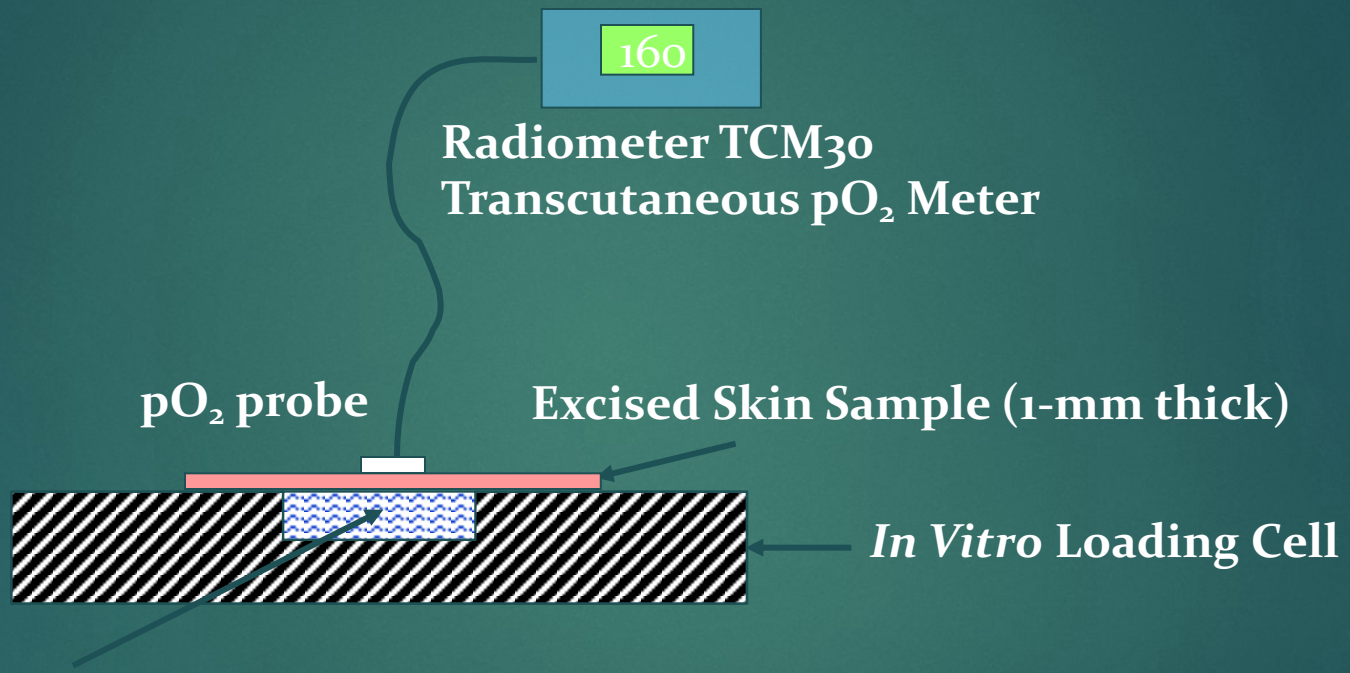
- Response:
- Unpublished ex vivo studies at Univ. of Miami showed increased subcutaneous oxygen tensions compared with vehicles.

- Following investigation:

Oxygen Emulsion Transfer

Bench Top Study Set-Up

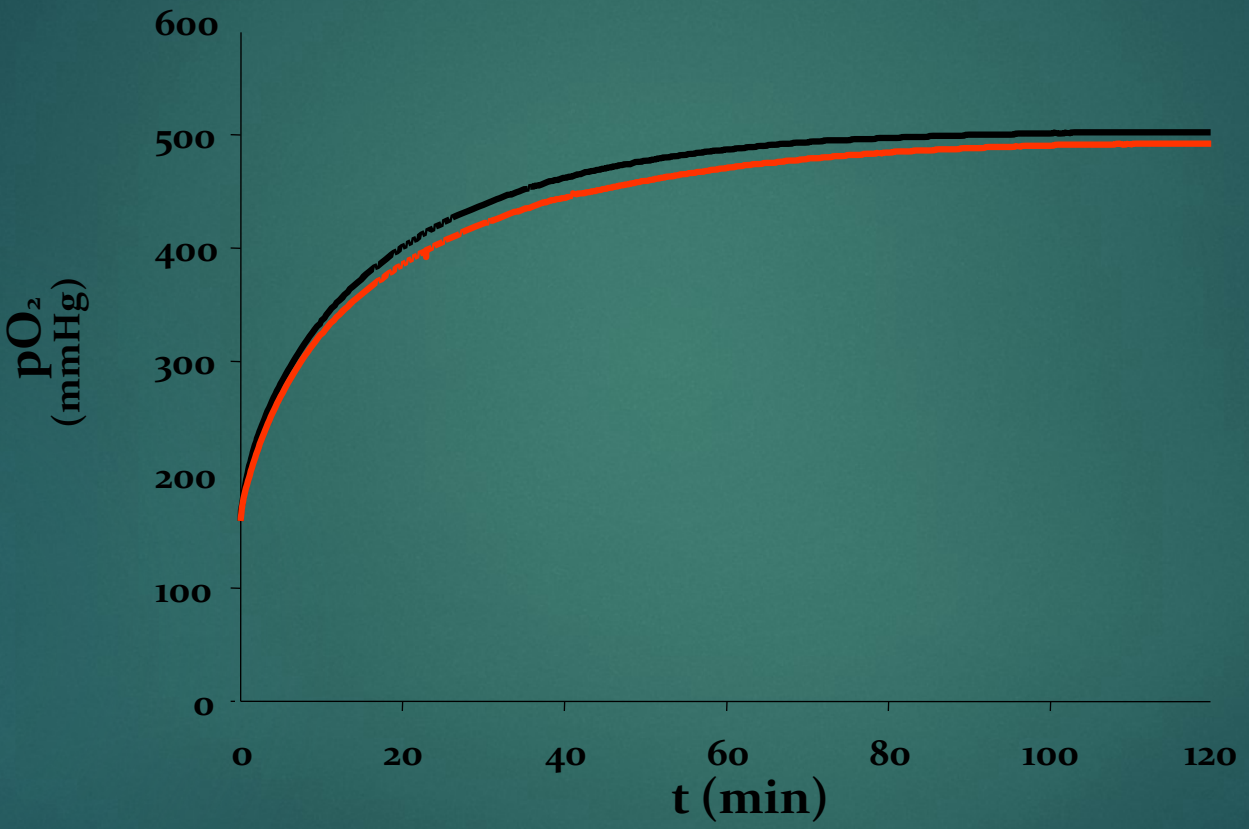
Baseline



<u>Test Well</u> – contains oxygenated emulsion
Well dimensions: 2.5 x 2.5 x 0.3 cm (depth)
~ approximately 2.0 ml capacity

Oxygen Emulsion Transfer

Bench Top Study Results



Research shows a **3-fold increase in measurable oxygen** which has passed through a 1mm thick piece of tissue.

Li, J: et al: Effects of a topical aqueous oxygen emulsion on collagen deposition and angiogenesis in a porcine deep partial-thickness wound model. *Exp Dermatol.*2013, 22, 656-681.

- Partial-thickness wound model evaluate effects of a supersaturated topical oxygen emulsion (TOE) on wound repair- compared to vehicle
- Semi- qualitative IF staining used to examine protein production for types I & III collagen and VEGF
- Histologic analysis performed
- Results:

1- TOE-treated wounds exhibited earlier and better signs of angiogenesis compared to wounds of vehicle alone control group ($p<0.01$)

2-IF results demonstrated wounds treated with TOE had significant stronger staining for all 3 proteins (types I & III collagen, VEGF) compared to control vehicle group

- Impression: Study suggests a TOE had beneficial impact on the proliferative phase of wound healing

Was the Vehicle responsible for the Results?

- The vehicle enhanced the rate of epithelialization in the porcine model –not surprising
- Prior studies have shown vehicles are not inhert and can either adversely or beneficially effect the healing process
- Both these studies (partial-wound and burn) TOE demonstrated a significant effect over vehicle alone

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Eaglestein, WH et al: "Inert vehicles do affect wound healing". *J Invest Dermatol* 1980;74(2):90-91.

Summary

- Initial pilot study of 10 patients treated with a TOE demonstrated remarkable improvement in reduction of post PDT anticipated side effects of edema, erythema, pain, and stinging when compared to the non-treated side
- TOE was safe producing zero AE (adverse effects)
- A TOE can increase the oxygen tension not only at the skin surface, but based on the available data- it goes deeper than surface depth
- The exact mechanism of improvement is unclear
- An increased oxygen tension is attractive and supported by 2 animal studies
- However, both studies were small and based on animal models

Summary -II

- Regardless of the mechanism, the clinical benefit of a TOE for patients having PDT proved extremely beneficial and improved acceptance of additional PDT treatments
- Further multicenter studies with larger numbers of patients to evaluate and validate these findings are needed.
- Physicians' ability to reduce post PDT morbidity should increase patient acceptance going forward
- Future: Study TOE application pre-PDT for "Turbo Boost" spot hypertrophic AKs however, 1st- we will look at actual oxygen levels all during PDT process to benchmark oxygen levels to determine TOE application time to predict clinical outcome.

Acknowledgments

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- Steven M. Kent BS
- Cutagenesis for supply of their topical oxygen emulsion