A COMPARISON OF TREATMENT OF PSORIASIS WITH ACITRETIN OR TAZAROTENE GEL 0.1% AND ACTIVE OR SHAM TREATMENTS WITH THE 308 NM EXCIMER LASER

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OUTLINE

- Background
- Methods
- Results
- Discussion
- Conclusion

BACKGROUND - PSORIASIS

- Psoriasis is a chronic inflammatory dermatosis afflicting ~3.2% of US adults[1]
- The disease clinically manifests as scaly papules and plaques and can involve all areas of the body[2]
- Treatment modalities are highly varied and include topical ointments and creams, UV light, oral medications, injectable medications and various combinations of these treatments[3]

1. RACHAKONDA TD, SCHUPP CW, ARMSTRONG AW. PSORIASIS PREVALENCE AMONG ADULTS IN THE UNITED STATES. J AM ACAD DERMATOL. 2014 JAN 2. EPUB AHEAD OF PRINT.
2. LANGLEY RGB, KRUEGER GG, GRIFFITHS CEM. PSORIASIS: EPIDEMIOLOGY, CLINICAL FEATURES, AND QUALITY OF LIFE. ANN RHEUM DIS 2005;64:II18-II23
3. LEBWOHL M, TING PT, KOO JYM. PSORIASIS TREATMENT: TRADITIONAL THERAPY. ANN RHEUM DIS 2005;64:II83-II86
4. PHOTO: HTTP://WWW.HEALTHLINE.COM/HEALTH-SLIDESHOW/PLAQUE-PSORIASIS-PICTURES#3

BACKGROUND – ACITRETIN AND TAZAROTENE

- **Acitretin** is a retinoic acid derivative used in the treatment of psoriasis
- It works by normalizing cellular differentiation and maturation
- It is an oral pill frequently used in combination with other psoriasis medications to enhance treatment and minimize side effects
- Side effects include teratogenicity, cheilitis, xerosis, myalgias/arthralgias, pseudotumor cerebri, hyperlipidemia, and hepatotoxicity

- **Tazarotene** is a retinoic acid derivative used in the treatment of psoriasis
- It works by normalizing cellular differentiation and maturation
- It is a topical cream frequently used in combination with other psoriasis medications to enhance treatment and minimize side effects
- Side effects include primarily local irritation of the skin

1. PILKINGTON T, BROGDEN RN. ACITRETIN. A REVIEW OF ITS PHARMACOLOGY AND THERAPEUTIC USE. DRUGS. 1992 APR;43(4):597-627.
2. LEBWOHL M, ALI S; TREATMENT OF PSORIASIS. PART 1. TOPICAL THERAPY AND PHOTOTHERAPY. J AM ACAD DERMATOL. 2001 OCT;45(4):487-98; QUIZ 499-502. REVIEW.

BACKGROUND – EXCIMER LASER

- UV light is a long used, effective therapy for the treatment of psoriasis[1]
- Narrow band UVB at a wavelength of 311 nm has proven to be a safe and effective treatment of psoriasis[1]
- The excimer laser delivers a highly focused, high energy pulse of light at 308 nm and has several advantages over Narrow Band UVB in limited plaque-type psoriasis[2]:
  - Safe and rapid delivery of treatment levels of energy to affected plaques
  - Focused delivery of energy to affected areas only
  - Deep penetration of energy into thick, scaly plaques
  - 77-90% improvements in PASI scores after 15 treatments as opposed to optimal treatment effect in 25-30 treatments with Narrow Band UVB

1. LAPOLLA W, YENTZER BA, BAGEL J, HALVORSON CR, FELDMAN SR. A REVIEW OF PHOTOTHERAPY PROTOCOLS FOR PSORIASIS TREATMENT. J AM ACAD DERMATOL. 2011 MAY;64(5):936-49
2. HE Y, ZHANG X, DONG J, XU J, WANG J. CLINICAL EFFICACY OF A 308 NM EXCIMER LASER FOR TREATMENT OF PSORIASIS VULGARIS. PHOTODERMATOL PHOTOIMMUNOL PHOTOMED 2007;23:238-241.

BACKGROUND - HYPOTHESIS

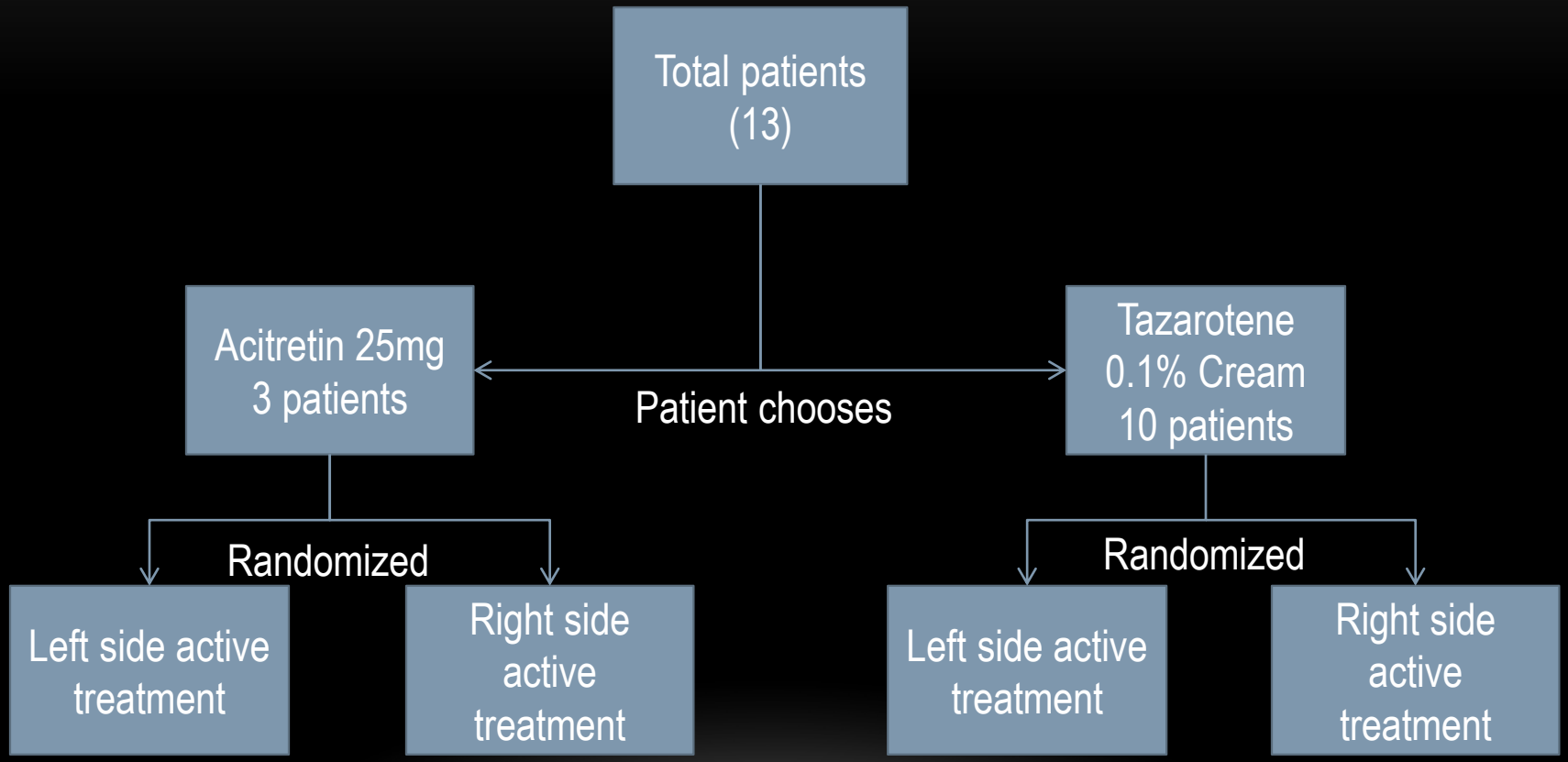
- Does dual treatment with the excimer laser in combination with topical or systemic retinoids result in greater improvements in psoriatic plaque clearance as measured by the National Psoriasis Foundation Psoriasis Score (NPF-PS) than treatment with either agent plus sham laser?

1. PHOTO SOURCE: RODEWALD EJ, HOUSMAN TS, MELLEN BG, FELDMAN SR. EFFICACY OF 308NM LASER TREATMENT OF PSORIASIS COMPARED TO HISTORICAL CONTROLS. DERMATOLOGY ONLINE JOURNAL 7(2):4, FIGURE 1 (URL: HTTPS://ESCHOLARSHIP.ORG/UC/ITEM/0VB021J9)

METHODS – STUDY DESIGN

- Randomized double-blind, intra-patient, left-to-right side comparison, parallel-group study
- Eligibility criteria:
  - Male and female subjects aged 18 and older
  - Stable, approximately anatomically symmetrical plaque type or palmar-planter psoriasis
  - Body surface area involvement of between 1 and 5 %
  - NPF-PS score of at least 8
- Exclusion criteria:
  - Fitzpatrick type I skin, on potentially photosensitizing medications, pregnancy
  - Use of systemic or phototherapy in the 4 weeks prior to entering the study
  - Use of biologic agents within 5 half-lives of the agent prior to entering the study
  - Use of topical therapies other than emolients 2 weeks prior to entering the study
  - Elevated liver enzymes, triglycerides, and women of childbearing potential in the acitretin arm

METHODS – STUDY DESIGN



METHODS - ASSESSMENT

- Primary endpoint: Percent change from baseline in the modified NPF-PS at week 12
- Secondary endpoints, percent change from baseline in:
  - The modified NPF-PS at weeks 3 and 8
  - Target Plaque Sum Score (TPSS) at weeks 3, 8, and 12
  - TPSS subscores (erythema, induration, scale) at weeks 3, 8, and 12
  - Palmoplanter Pustulosis Severity Index (PPPASI) at weeks 3, 8, and 12
  - The number of excimer laser treatments, time, and cumulative energy required to achieve an average TPSS of 0 to 1

METHODS – STATISTICAL ASSESSMENT

- Power calculation is based on prior efficacy data from studies of excimer, tazarotene, and acitretin[1,2,3]:
  - Power = 0.8, Alpha = 0.05, Delta = 0.1, Sigma = 0.15
  - The number needed to treat to detect a difference in the excimer vs sham laser treatments was estimated at 20 patients per arm based on these assumptions
- The blinded portion of the study was analyzed as two separate, independent studies: the actitretin arm and the tazarotene arm
- Paired t-testing was used to analyze each of the primary and secondary endpoints
- Statistical significance was demonstrated if the p-value for the difference between the active and the sham treatments was less than 0.05

1. HE YL, ZHANG XY, DONG J, XU JZ, WANG J. CLINICAL EFFICACY OF A 308 NM EXCIMER LASER FOR TREATMENT OF PSORIASIS VULGARIS. PHOTODERMATOL PHOTOIMMUNOL PHOTOMED. 2007 DEC;23(6):238-41.
2. BEHRENS S, GRUNDMANN-KOLLMANN M, SCHIENER R, PETER RU, KERSCHER M. COMBINATION PHOTOTHERAPY OF PSORIASIS WITH NARROW-BAND UVB IRRADIATION AND TOPICAL TAZAROTENE GEL. J AM ACAD DERMATOL. 2000 MAR;42(3):493-42.
3. CARLIN CS, CALLIS KP, KRUEGER GG. EFFICACY OF ACITRETIN AND COMMERCIAL TANNING BED THERAPY FOR PSORIASIS. ARCH DERMATOL. 2003 APR;139(4):436-42.

RESULTS - PRIMARY ENDPOINT: NPF-PS

	Acitretin				Tazarotene			
Time (week)	Active Mean Change (%)	Sham Mean Change (%)	Percent Difference between Active and Sham (%, 95% CI)	P-value	Active Mean Change (%)	Sham Mean Change (%)	Percent Difference between Active and Sham (%, 95% CI)	P-value
3	-26.0	-26.0	0 (0, 0)	n/a	-14.5	-13.8	-0.7 (-4.4, 3.0)	0.673
8	-64.0	-52.1	-11.9 (-37.7, 13.9)	0.185	-32.7	-26.9	-5.8 (-11.3, -0.2)	0.045
12	-70.6	-67.3	-3.4 (-27.4, 20.7)	0.607	-30.9	-27.9	-3.0 (-11.9, 5.8)	0.446

RESULTS – SECONDARY ENDPOINTS: TPSS

	Acitretin				Tazarotene			
Time (week)	Active Mean Change (%)	Sham Mean Change (%)	Percent Difference between Active and Sham (%, 95% CI)	P-value	Active Mean Change (%)	Sham Mean Change (%)	Percent Difference between Active and Sham (%, 95% CI)	P-value
3	-16.7	-20	3.3 (-11.0, 17.7)	0.423	-17.3	-16.6	-0.7 (-8.4, 7.0)	0.845
8	-56.7	-45.8	-10.8 (-90.9, 69.3)	0.620	-28.5	-40.3	11.9 (-1.4, 25.2)	0.074
12	-64.2	-62.5	-1.7 (-57.7, 54.3)	0.910	-30.9	-41.4	10.5 (-5.7, 26.7)	0.170

DISCUSSION – ACITRETIN ARM

- A review of the literature shows improvements from baseline scores of approximately 50%[1,2]
- One study involving both UV light and acitretin showed improvement in baseline scores of 79%[3]
- This study showed improvements of approximately 70% in both arms of the study

1. CARLIN CS, CALLIS KP, KRUEGER GG. EFFICACY OF ACITRETIN AND COMMERCIAL TANNING BED THERAPY FOR PSORIASIS. ARCH DERMATOL. 2003 APR;139(4):436-42.
2. MITTAL R, MALHOTRA S, PANDHI P, KAUR I, DOGRA S. EFFICACY AND SAFETY OF COMBINATION ACITRETIN AND PIOGLITAZONE THERAPY IN PATIENTS WITH MODERATE TO SEVERE CHRONIC PLAQUE-TYPE PSORIASIS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL. ARCH DERMATOL. 2009 APR;145(4):387-93.
3. VAN DE KERKHOF PC, CAMBAZARD F, HUTCHINSON PE, HANEKE E, ET AL. THE EFFECT OF ADDITION OF CALCIPOTRIOL OINTMENT (50 MICROGRAMS/G) TO ACITRETIN THERAPY IN PSORIASIS. BR J DERMATOL. 1998 JEN;138(1):84-9.

DISCUSSION – TAZAROTENE ARM

- Responses for tazarotene 0.1% gel vary widely in the literature, from approximately 20 to 75% improvement from baseline[1,2,3]
- Studies using tazarotene gel and UV light show improvements from baseline from approximately 50 to 65%[4,5]
- This study showed improvements from baseline of approximately 30%

1. KUMAR U, KAUR I, DOGRA S, DE D, KUMAR B. TOPICAL TAZAROTENE VS. COAL TAR IN STABLE PLAQUE PSORIASIS. CLIN EXP DERMATOL. 2010 JUL;35(5):482-6.
2. GREEN L, SADOFF W. A CLINICAL EVALUATION OF TAZAROTENE 0.1% GEL, WITH AND WITHOUT A HIGH- OR MID-HIGH-POTENCY CORTICOSTEROID, IN PATIENTS WITH STABLE PLAQUE PSORIASIS. J CUTAN MED SURG. 2002 MAR-APR;6(2):95-102.
3. LEBWOHL M, AST E, CALLEN JP, CULLEN SI, ET AL. ONCE-DAILY TAZAROTENE GEL VERSUS TWICE-DAILY FLUOCINONIDE CREAM IN THE TREATMENT OF PLAQUE PSORIASIS. J AM ACAD DERMATOL. 1998 MAY;38(5 PT 1):705-11.
4. BEHRENS S, GRUNDMANN-KOLLMANN M, SCHIENER R, PETER RU, KERSCHER M. COMBINATION PHOTOTHERAPY OF PSORIASIS WITH NARROW-BAND UVB IRRADIATION AND TOPICAL TAZAROTENE GEL. J AM ACAD DERMATOL. 2000 MAR;42(3):493-5.
5. SCHIENER R, BEHRENS-WILLIAMS SC, PILLEKAMP H, KASKEL P, PETER RU, KERSCHER M. CALCIPOTRIOL VS. TAZAROTENE AS COMBINATION THERAPY WITH NARROWBAND ULTRAVIOLET B (311 NM): EFFICACY IN PATIENTS WITH SEVERE PSORIASIS. BR J DERMATOL. 2000 DEC;143(6):1275-8.

DISCUSSION - ANALYSIS

- The primary limitation of this study is the small sample size
- Due to similar responses in both the sham and active treatment sides, it is likely the laser energy escalation protocol was inadequate
- The clinical assessment tools have a large subjective component and may not be sensitive enough to detect small differences in treatment effects

CONCLUSIONS

- The 308 nm excimer laser is a unique and interesting tool in the armamentarium against psoriasis, but using a conservative dose escalation protocol does not lead to significant improvements in plaque clearance over those achieved by topical or systemic retinoids alone.
- Further studies are needed to determine if the synergistic effects observed between retinoids and narrow band UV light therapy can be reproduced using the excimer laser by using more aggressive laser energy dose escalation protocols.