

Novel Acne Treatments

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Disclosures

Almiral – A(H)

Dermira – A(H)

Sonoma pharmaceuticals A(H)

Outline

- PDT with ALA daylight
- Gold particle/laser/light
- Supplements
- Probiotics

- ON THE HORIZON
- Clascoterone (antiandrogen)
- Vaccines
- Phages

Daylight PDT with ALA gel

- METHODS:
 - 20 patient with mild to moderate acne treated with 5% delta-aminolevulinic acid, treated every 2 weeks for 4 total times
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- Del Duca E, Manfredini M, Petrini N, Farnetani F, Chester J, Bennardo L, Schipani G, Tamburi F, Sannino M, Cannarozzo G, Pellacani G, Nisticó SP. Daylight Photodynamic Therapy with 5-aminolevulinic acid 5% gel for the treatment of mild-to-moderate inflammatory acnG Ital Dermatol Venereol. 2019 Sep 12. doi: 10.23736/S0392-0488.19.06392-2. [Epub ahead of print]

Daylight PDT with ALA gel

- Compared to T0, mean inflammatory lesions count decreased in all patients at FU1, from 16.7 ± 4.4 to 5.2 ± 3.3 (p).
 - No adverse events were reported and no patients were lost to follow-up.
 - PGA results of "excellent" or "good" improvement were reported in 95% at T3 and 90% at FU1.
 - Patients' self-assessments was 7.6 ± 1.0 (T3). Discomfort was 0.5 ± 0.2 (T3 and FU1)
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- Del Duca E, Manfredini M, Petrini N, Farnetani F, Chester J, Bennardo L, Schipani G, Tamburi F, Sannino M, Cannarozzo G, Pellacani G, Nisticó SP. Daylight Photodynamic Therapy with 5-aminolevulinic acid 5% gel for the treatment of mild-to-moderate inflammatory acnG Ital Dermatol Venereol. 2019 Sep 12. doi: 10.23736/S0392-0488.19.06392-2. [Epub ahead of print]

Daylight PDT with ALA gel

- DL-PDT seems to be an effective and tolerable therapy for the treatment of mild to-severe inflammatory acne.
- Is a novel therapy to employ

Gold particles

- Novel acne treatment based on selective photothermolysis of pilosebaceous units with follicular delivery of inert gold microparticles as an exogenous chromophore and diode laser pulses has been developed.
- Recent study

Gold Particles

- Moderate and moderately severe facial acne
- Open-label, pilot study
- Single treatment regimen consisted of three weekly facial treatments with topically applied gold microparticles and diode laser pulses.

- Fuchs CSK, Bay C, Adatto M, Lomholt H, Haedersdal M. Acne Treatment With Light Absorbing Gold Microparticles and Optical Pulses: An Open-Label European Multi-Centered Study in Moderate to Moderately Severe Acne Vulgaris Patients. *Lasers Surg Med.* 2019 Oct;51(8):686-693.

Gold Particles

- 28 patients were enrolled in the study
 - 25 patients completed study with single treatment
 - After a single monotherapy treatment regimen, 76% patients (19/25) achieved $\geq 40\%$ reduction in WLC (mean WLC reduction: 63%; SD: 13%).
 - After 2 two treatment regimens (n = 9 patients), 56% experienced a reduction in acne lesion burden (WLC) $\geq 40\%$ at 24 weeks and 89% 36 weeks post-baseline.
 - Mean pain score was 4.0 (SD: 1.3), and transient erythema and perifollicular edema were commonly noted after treatment. Most patients (81%) were either "satisfied" or "very satisfied" with the treatment.
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- Fuchs CSK, Bay C, Adatto M, Lomholt H, Haedersdal M. Acne Treatment With Light Absorbing Gold Microparticles and Optical Pulses: An Open-Label European Multi-Centered Study in Moderate to Moderately Severe Acne Vulgaris Patients. *Lasers Surg Med.* 2019 Oct;51(8):686-693.

Gold particles

- Acne therapy based on selective photothermolysis with gold microparticles shows promise and may be used in treatment of moderate to moderately severe acne.

- Fuchs CSK, Bay C, Adatto M, Lomholt H, Haedersdal M. Acne Treatment With Light Absorbing Gold Microparticles and Optical Pulses: An Open-Label European Multi-Centered Study in Moderate to Moderately Severe Acne Vulgaris Patients. *Lasers Surg Med.* 2019 Oct;51(8):686-693.

Dual IPL device

- **BACKGROUND AND OBJECTIVE:**
- Study aimed to assess the clinical safety and efficacy of a novel dual-band “notch” acne filter (400-600nm and 800-1200nm) in improving inflammatory and non-inflammatory lesions in patients presenting with mild-to-moderate acne.
- Knight JM. Combined 400-600nm and 800-1200nm Intense Pulsed Phototherapy of Facial Acne Vulgaris. *J Drugs Dermatol.* 2019 Nov 1;18(11):1116-1122.

Dual IPL device

- Single-site, prospective study of 10 patients with Fitzpatrick skin types II-V presenting with mild to moderate inflammatory facial acne vulgaris.
 - Five (5) whole-face light treatments were conducted at 1-2-week intervals with an IPL system (Lumenis M22 System, Lumenis Ltd.) equipped with a dual-band “notch” acne filter (400-600nm and 800-1200nm).
 - Follow-up visits were performed at 1 and 4 weeks following the last treatment session.
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- Knight JM. Combined 400-600nm and 800-1200nm Intense Pulsed Phototherapy of Facial Acne Vulgaris. *J Drugs Dermatol*. 2019 Nov 1;18(11):1116-1122.

Dual IPL device

- Acne mean change from baseline was assessed using the 4-point Investigator Global Assessment (IGA) scale.
 - Comprehensive facial photographs were taken, and lesions were counted at screening, treatment 4, and both 1- and 4-week follow-up visits.
 - The investigator and the patients assessed overall improvements in appearance, using the 5-point Likert scale. Subjects also completed the Cardiff Acne Disability Index (CADI) questionnaire and rated their satisfaction from treatment. Subject-reported pain, using the visual analog scale (VAS), and downtime were also recorded.
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- Knight JM. Combined 400-600nm and 800-1200nm Intense Pulsed Phototherapy of Facial Acne Vulgaris. *J Drugs Dermatol*. 2019 Nov 1;18(11):1116-1122.

Dual IPL device

- Treatment impact on overall lesion clearance was most substantial at 4 weeks follow-up, at which 50% of patients showed at least a 50% reduction from baseline of lesion counts ($P < 0.0001$).
- IGA scores improved throughout the course of the study, and significant improvements in the overall skin condition was noted, with mean 1.63-point and 1.50-point increases from baseline in the acne improvement ratings, at 1- and 4-weeks follow-up, respectively ($P = 0.0074, 0.0063$).
- Patient-assessed CADl improved throughout the treatment and follow-up visits, peaking at a 3.22-point and 4.9-point average reductions from baseline at 1-week follow-up ($P = 0.0001$) and 1-month follow-up ($P < 0.0001$), respectively.
- The majority of the patients (80%) rated their acne lesions as improved, much improved, or very much improved at 4-weeks follow-up ($P = 0.0004$). Significant enhancements were also noted for skin texture.
- Eighty percent of the patients reported overall satisfaction with treatment outcomes, while 60% rated their satisfaction as “good” or “very good” at 4-weeks follow-up ($P < 0.0001$). Treatments were well tolerated, with mean per-session VAS scores being ≤ 3.77 , while the mean downtime was negligible (a few hours).
- Knight JM. Combined 400-600nm and 800-1200nm Intense Pulsed Phototherapy of Facial Acne Vulgaris. J Drugs Dermatol. 2019 Nov 1;18(11):1116-1122.

Oral supplements – differences between males and females

- Skin care line with one oral supplement for men and a different oral supplement for women as well as a topical cream device.
- Studies for the treatment of mild to moderate acne
- For males - biotin, probiotic, vitamin E, zinc, nicotinamide and **beta sitosterol and Boswellia serrata**
- For females - biotin, probiotic, vitamin E, zinc, nicotinamide and **myo-inositol and folic acid**.
- The topical cream device is represented by the association between active plant agents (verbascoside, *Ocimum gratissimum*) and keratolytic molecules (salicylic acid, gluconolactone, complex alpha-hydroxy acids).
- Tolino E, Skroza N, Mambrin A, Bernardini N, Zuber S, Balduzzi V, Marchesiello A, Proietti I, Potenza C. Novel combination for the treatment of acne differentiated based on gender: a new step towards personalized treatment. *G Ital Dermatol Venereol.* 2018 Dec;153(6):866-871

Oral supplements – differences between males and females

- An equal number of male and female patients with mild to moderate acne
 - Double-blinded
 - Graded at were enrolled in a double-blinded clinical trial. Efficacy and tolerability evaluations were performed at week 4 (T1) and week 12 (T2) by Global acne Grading System (GAGS)
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- Tolino E, Skroza N, Mambrin A, Bernardini N, Zuber S, Balduzzi V, Marchesiello A, Proietti I, Potenza C. Novel combination for the treatment of acne differentiated based on gender: a new step towards personalized treatment. *G Ital Dermatol Venereol.* 2018 Dec;153(6):866-871

- RESULTS:

- Most of patients had satisfactory therapeutic response, in terms of GAGs reduction. All the four groups presented a statistically significant improvement of the mean GAGs at T2 but those assuming the oral supplement improved more, as expected.

- CONCLUSIONS:

- Our data suggest that this association can be considered a new effective option for mild and moderate acne. This therapeutic line differs from others in the gender matched oral treatment.
- Tolino E, Skroza N, Mambrin A, Bernardini N, Zuber S, Balduzzi V, Marchesiello A, Proietti I, Potenza C. Novel combination for the treatment of acne differentiated based on gender: a new step towards personalized treatment. *G Ital Dermatol Venereol.* 2018 Dec;153(6):866-871

Topical myoinositol

- Uncontrolled, open-label clinical study
- Forty (40) Caucasian patients with Adult Female Acne
- Measured:
 - lesion counts
 - sebum production
 - Global Acne Grading System (GAGS) scale endpoints
- Measured changes from baseline to the end of treatment in androgen and beclin-1 levels (as a marker of autophagy) in skin biopsy supernatants.
- Fabbrocini G, Capasso C, Donnarumma M, Cantelli M, Le Maître M, Monfrecola G, Emanuele E. A peel-off facial mask comprising myoinositol and trehalose-loaded liposomes improves adult female acne by reducing local hyperandrogenism and activating autophagy. *J Cosmet Dermatol*. 2017 Dec;16(4):480-484.

Topical myoinositol

- The mean counts of comedones, papules, pustules, and nodular lesions decreased significantly (all $P < .001$).
- The mean Sebutape[®] score was reduced from 3.4 ± 0.6 to 1.8 ± 0.2 ($P < .001$),
- The GAGS scale score decreased from 16.8 ± 5.3 at baseline to 9.8 ± 4.6 after treatment ($P < .001$).
- A significant decrease in testosterone and dehydroepiandrosterone sulfate in skin biopsy supernatants was observed, whereas beclin-1 levels increased significantly ($P < .001$).
- **Conclusion:**
- A ready-to-use peel-off facial mask containing myoinositol and trehalose-loaded liposomes improved the cosmetic appearance of Adult Female Acne
- Fabbrocini G, Capasso C, Donnarumma M, Cantelli M, Le Maître M, Monfrecola G, Emanuele E. A peel-off facial mask comprising myoinositol and trehalose-loaded liposomes improves adult female acne by reducing local hyperandrogenism and activating autophagy. *J Cosmet Dermatol.* 2017 Dec;16(4):480-484.

Myoinositol (Inositol) Story

- Fifty (50) patients with Polycystic Ovarian Syndrome (PCOS)
- BMI, LH, FSH, insulin, HOMA index, androstenedione, testosterone, free testosterone, **hirsutism and acne** were evaluated at 0,3, 6 months.
- After **3 months** of MYO administration, plasma LH, testosterone, free testosterone, insulin and HOMA index resulted significantly reduced; no significant changes were observed in plasma FSH and androstenedione levels.
- Both hirsutism and acne decreased after **6 months** of therapy.

- DISCUSSION:
- MYO administration is a simple and safe treatment that ameliorates the metabolic profile of patients with PCOS, reducing hirsutism and acne.
- Zacchè MM1, Caputo L, Filippis S, Zacchè G, Dindelli M, Ferrari A. Efficacy of myo-inositol in the treatment of cutaneous disorders in young women with polycystic ovary syndrome. *Gynecol Endocrinol.* 2009 Aug;25(8):508-13.

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Myo-inositol vs. d-chiro inositol

- Both are second messengers in the signal transduction of insulin
- **Myo-inositol** promotes the entry of glucose into the cell
- **D-chiro inositol** rules the conversion of glucose to glycogen

Myo-inositol vs. d-chiro inositol

- Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women in fertile age.
- PCOS is characterized by oligo-anovulation, hyperandrogenism and insulin-resistance.
- Dermatologic findings include acne and hirsutism
- Various therapeutic approaches have been used including diet, oral contraceptives (OCs) or anti-androgens.
- Inositol has recently been used in this setting as a treatment of insulin resistance.

Myo-inositol vs. d-chiro inositol

- Study of 137 women with polycystic ovarian syndrome (PCOS) after 6 months of
 - myo-inositol
 - D-chiro-inositol
 - Placebo
- Clinical, endocrine and metabolic response including oligomenorrhea and/or acne and/or mild hirsutism and insulin-resistance were evaluated.
- Myo-inositol (MI-PG) and D-chiro inositol (DCI-PG) significantly improved the following in young, overweight, PCOS patients:
 - the regularity of the menstrual cycle
 - the Acne Score,
 - the endocrine and metabolic parameters
 - the insulin-resistance
- Pezza M, Carlomagno V, Casucci G. Inositol and acne. *G Ital Dermatol Venereol.* 2015 Dec;150(6):649-53. Epub 2014 Jul 31

Myo-inositol vs. d-chiro inositol

- Myo-inositol (MI-PG) and D-chiro inositol (DCI-PG) significantly improved the following in young, overweight, PCOS patients:
 - the regularity of the menstrual cycle
 - **the Acne Score**
 - the endocrine and metabolic parameters
 - the insulin-resistance

Myo-inositol vs. d-chiro inositol

- Authors conclude myo-inositol and with D-chiro inositol could be proposed as a potential valid therapeutic approach for the treatment of patients with PCOS and acne. Additionally, further examination and for a longer period of treatment are needed

- Pezza M, Carlomagno V, Casucci G. Inositol and acne. G Ital Dermatol Venereol. 2015 Dec;150(6):649-53. Epub 2014 Jul 31

The Probiotic Question?

Probiotics?

- Forty-five 18- to 35-year-old females with acne
 - Assigned to one of 3 groups
 - Group A **probiotic supplementation**
 - Group B **minocycline only**
 - Group C **both (probiotic and minocycline)**
 - Assessed at 2-, 4-, 8-, and 12-week follow-up visits
-
- Jung GW, Tse JE, Guiha I, Rao J. Prospective, randomized, open-label trial comparing the safety, efficacy, and tolerability of an acne treatment regimen with and without a probiotic supplement and minocycline in subjects with mild to moderate acne. *J Cutan Med Surg.* 2013 Mar-Apr;17(2):114-22.

Probiotics?

- Probiotics may be considered a therapeutic option or adjunct for acne vulgaris
 - Possibly providing a synergistic anti-inflammatory effect
 - Reducing potential adverse events secondary to chronic antibiotic use
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- Jung GW, Tse JE, Guiha I, Rao J. Prospective, randomized, open-label trial comparing the safety, efficacy, and tolerability of an acne treatment regimen with and without a probiotic supplement and minocycline in subjects with mild to moderate acne. *J Cutan Med Surg.* 2013 Mar-Apr;17(2):114-22.

Probiotics?

- **All patients demonstrated a significant improvement in total lesion count 4 weeks after treatment initiation ($p < .001$), with continued improvement seen with each subsequent follow-up visit ($p < .01$).**
- At the 8- and 12-week follow-up visits, group C (**combination group**) had a significant decrease in total lesion count versus groups A ($p < .001$) and B ($p < .01$).
- Two patients (13%) from group B (**minocycline only group**) failed to complete the study secondary to **vaginal candidiasis**.
- Jung GW, Tse JE, Guiha I, Rao J. Prospective, randomized, open-label trial comparing the safety, efficacy, and tolerability of an acne treatment regimen with and without a probiotic supplement and minocycline in subjects with mild to moderate acne. *J Cutan Med Surg.* 2013 Mar-Apr;17(2):114-22.

Probiotics?

Basic Science Evidence

- A pilot, randomized, double-blinded, placebo-controlled study was conducted with 20 adult subjects
- Two groups
 - **probiotic group**, *Lactobacillus rhamnosus* SP1 (LSP1)
 - **placebo group**
- Paired skin biopsies – before and after 12 week treatment
- Analyzed for insulin-like growth factor 1 (IGF1) and forkhead box protein O1 (FOXO1) gene expression
- Fabbrocini G, Bertona M, Picazo Ó, Pareja-Galeano H, Monfrecola G, Emanuele E. Supplementation with *Lactobacillus rhamnosus* SP1 normalises skin expression of genes implicated in insulin signalling and improves adult acne. *Benfer Microbes*. 2016 Nov 30;7(5):625-630.

Probiotics?

Basic Science Evidence

- Compared with baseline, the probiotic group showed:
 - 32% (P<0.001) reduction in IGF-1
 - 65% increase (P<0.001) in FOXO1 gene
- No such differences were observed in the placebo group

- Fabbrocini G, Bertona M, Picazo Ó, Pareja-Galeano H, Monfrecola G, Emanuele E. Supplementation with *Lactobacillus rhamnosus* SP1 normalises skin expression of genes implicated in insulin signalling and improves adult acne. *Benfer Microbes*. 2016 Nov 30;7(5):625-630.

Probiotics?

Basic Science Evidence

- **Clinically**, based on a five-point rating scale, the probiotic group
 - **Adjusted odds ratio of 28.4** (95% confidence interval = 2.2-411.1, $P < 0.05$) to be rated by physicians as improved/markedly improved (versus worsened or unchanged) compared with the placebo group
- Authors conclude that this probiotic supplementation may normalize expression of genes involved in adult acne.
- Fabbrocini G, Bertona M, Picazo Ó, Pareja-Galeano H, Monfrecola G, Emanuele E. Supplementation with *Lactobacillus rhamnosus* SP1 normalises skin expression of genes implicated in insulin signalling and improves adult acne. *Benfer Microbes*. 2016 Nov 30;7(5):625-630.

Topical Probiotics

- Popular idea
 - Need more information
-
- Lee GR, Maarouf M, Hendricks AJ, Lee DE, Shi VY¹. **Topical probiotics: the unknowns behind their rising popularity.** Dermatol Online J. 2019 May 15;25(5).

New anti-androgen - Clascoterone

- Cortexolone 17 α -propionate (clascoterone) is a novel topical androgen antagonist that is being analyzed for its ability to treat acne.
- Clascoterone is a potent antiandrogen that is well tolerated and has selective topical activity.
- Its potency as an acne therapeutic is currently being analyzed in a large phase 3 clinical trial.

- Rosette C, Agan FJ, Mazzetti A, Moro L, Gerloni M. Cortexolone 17 α -propionate (Clascoterone) Is a Novel Androgen Receptor Antagonist that Inhibits Production of Lipids and Inflammatory Cytokines from Sebocytes In Vitro. *J Drugs Dermatol*. 2019 May 1;18(5):412-418

New anti-androgen - Clascoterone

- Mechanism of action:
- Clascoterone was found to bind the androgen receptor (AR) with high affinity in vitro, inhibit AR-regulated transcription in a reporter cell line, and antagonize androgen-regulated lipid and inflammatory cytokine production in a dose-dependent manner in human primary sebocytes.
- When compared to another AR antagonist, spironolactone, clascoterone was significantly better at inhibiting inflammatory cytokine synthesis from sebocytes. Therefore, clascoterone may be an excellent candidate to be the first topical antiandrogen to treat acne.
- Rosette C, Agan FJ, Mazzetti A, Moro L, Gerloni M. Cortisolone 17 α -propionate (Clascoterone) Is a Novel Androgen Receptor Antagonist that Inhibits Production of Lipids and Inflammatory Cytokines from Sebocytes In Vitro. *J Drugs Dermatol*. 2019 May 1;18(5):412-418

Vaccine for Acne?

Vaccine for acne

- The severity of acne vulgaris is highly associated with the inflammatory response to Propionibacterium acnes (*P. acnes*) now referred to as Cutibacterium acnes (*C. acnes*)
- Create acne vaccines targeting secreted virulence factors of *C. acnes* including secretory Christie-Atkins-Munch-Peterson (CAMP) factor.
- Neutralization of secreted virulence factors by either active or passive vaccination

- Keshari S, Kumar M, Balasubramaniam A, Chang TW, Tong Y, Huang CM. Prospects of acne vaccines targeting secreted virulence factors of Cutibacterium acnes. Expert Rev Vaccines. 2019 May;18(5):433-437

Vaccine for acne

- Targeting secreted virulence factors without disturbing the commensal relationship.
- Future therapeutic monoclonal antibodies can be designed to specifically neutralize virulence factors of *C. acnes* including CAMP factors **without disrupting** the optimal balance of *C. acnes* in the human skin microbiome and lowering the risk of creating drug-resistant *C. acnes*
- Keshari S, Kumar M, Balasubramaniam A, Chang TW, Tong Y, Huang CM. Prospects of acne vaccines targeting secreted virulence factors of Cutibacterium acnes. Expert Rev Vaccines. 2019 May;18(5):433-437

What's on the horizon? Phages?

- Phage therapy against *P. acnes*
- Bacteriophages are bacterial viruses that naturally control microbial populations
- Known phages that can work against *P. acnes*
- Need more knowledge
- May play a role in the future in the treatment of acne