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Open-Label Evaluation of 5% Benzoyl Peroxide/1% Clindamycin Gel Used in Combination With Tazarotene 0.1% Cream and Oral Minocycline in the Treatment of Severe Acne Vulgaris

Emil A. Tanghetti, M.D.

Center for Dermatology and Laser Surgery, Sacramento, CA

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ABSTRACT

Background: The patient profile of severe acne most likely to respond to systemic therapy rather than topical therapy has been previously defined. Systemic antimicrobials and retinoids, alone or in combination, have been used to address the 4 main factors involved in the development of acne: excessive follicular keratinization,[1] hyperactivity of the sebaceous gland, proliferation of *Propionibacterium acnes*, and perifollicular inflammation.

Objective: I sought to gain preliminary efficacy data of topical benzoyl peroxide 5%/clindamycin 1% used in combination with tazarotene 0.1% cream and oral minocycline (75-100 mg/BID for female patients and 100 mg/BID for male patients) for patients with severe acne vulgaris that fit the criteria for treatment with systemic retinoid therapy.

Methods: 14 subjects with severe, refractory, nodular facial acne vulgaris were entered into the study and characterized by the following criteria: at least 30 facial inflammatory lesions (papules plus pustules); at least 10 facial noninflammatory lesions (open/closed comedones); stable disease, non-rapidly regressing facial acne vulgaris; no more than 10 facial inflammatory lesions that are larger than 5 mm in diameter; and a few inflammatory lesions that are suppurative and/or hemorrhagic. Lesion counts and photographs are used to document efficacy after 4, 8 and 12 weeks of treatment. The efficacy data are compared with historic response rates for systemic retinoid therapy reported in the literature.

Conclusions: While the patient profile of patients with severe acne most likely to respond to systemic retinoid therapy has been clearly defined, combinations of therapies that may provide an alternative therapy with fewer potential adverse effects warrant further investigation in this patient group.

INTRODUCTION

Acne vulgaris is the most common form of acne and is characterized by a mixture of inflammatory lesions and non-inflammatory lesions. Combination products containing 5% benzoyl peroxide and 1% clindamycin are an effective topical treatment for acne vulgaris.[1] Both components of these products have been shown to have in vitro activity against *P. acnes* bacteria.[1] By reducing the *P. acnes* bacteria colonies, the inflammatory process is minimized and clearing of acne lesions is enhanced. Retinoids, such as tazarotene, are also effective against acne vulgaris and are valuable in preventing the development of new microcomedones.[1]

Local topical therapy is generally assumed to be insufficient to adequately control severe acne and systemic treatment is indicated. Systemic antibiotics such as minocycline have been used to treat inflammatory acne for many years,[2] with oral minocycline commonly administered at a dose of 100 mg BID. Systemic isotretinoin is also very effective for the treatment of severe acne,[1] but it is associated with potentially significant adverse effects.

Most dermatology practices treat acne using combination therapy based on clinical experience. However, the literature contains only a few reports of the efficacy and tolerability of combination therapy (such as studies evaluating tazarotene in conjunction with one of the following: benzoyl peroxide,[3] clindamycin,[3] benzoyl peroxide/clindamycin,[4] or minocycline[5]). These combinations of two or three active agents offer good efficacy but it is possible that using all four of these agents in combination may further enhance efficacy—thereby potentially offering an alternative therapeutic approach for severe acne and one which has a superior safety profile to systemic isotretinoin. (For historical reference, it has been reported that 75% of subjects treated with systemic isotretinoin for 16 weeks had a 50% or greater improvement in acne with 80-90% reduction in total lesion count.[6] Adverse events occurred frequently, with 90-97% of subjects reporting cheilitis, 48-76% facial dermatitis, 29-44% epistaxis, 29-40% desquamation, 17-28% arthralgia, 0-30% conjunctivitis, and 5-16% malaise after either 0.1, 0.5, or 1.0 mg/kg bw.)

This study sought to gain preliminary efficacy data relating to the use of topical benzoyl peroxide 5%/clindamycin 1% gel in combination with tazarotene 0.1% cream and oral minocycline in patients with severe acne vulgaris who fit the criteria for treatment with systemic retinoid therapy. This investigation is important given the anticipated restrictions for the use of systemic isotretinoin.

OBJECTIVE

To evaluate the safety and effectiveness of 5% benzoyl peroxide/1% clindamycin gel used in combination with tazarotene 0.1% cream and oral minocycline in subjects with severe acne vulgaris.

METHODS

Key Inclusion Criteria

- Male or female, at least 12 years of age
- Severe facial acne vulgaris, unresponsive to systemic antibiotics used alone and characterized by the following:
  - ► At least 30 facial inflammatory lesions (papules plus pustules)
  - ► At least 10 facial non-inflammatory lesions (open/closed comedones)
  - ► ≤10 facial inflammatory lesions larger than 5 mm in diameter
  - ► A few inflammatory lesions that are suppurative and/or hemorrhagic
  - ► Stable disease (non-rapidly regressing).
- Females of childbearing potential required to have a negative urine pregnancy test at baseline and to practice a reliable method of contraception throughout the study
- Signed written informed consent

Key Exclusion Criteria

- Severe active acne scarring, cystic inflammatory lesions, sinus tracts, acne fulminans, or systemic signs of toxicity
- History of colitis, antibiotic-associated pseudomembranous colitis, erythema multiforme, lupus erythematosus, Stevens-Johnson syndrome, increased intracranial pressure, photosensitivity reactions (exaggerated sunburn), esophagitis, or liver, kidney, or hematopoietic abnormalities
- Known hypersensitivity to fluoromycin or tetracycline or any component of the test medications
- Insulin-dependent diabetes, any uncontrolled systemic disease, current or recent episode of mononucleosis, history of positive results for FANA test, DNA antibodies, or antineutrophil cytoplasmic antibodies
- Current or past history of abnormal pigmentation of the skin or mucous membranes due to minocycline
- Regular use of vitamin A (>5000 IU), anticoagulants, divalent cationic antacids, penicillin, iron, digoxin, bismuth subsalicylate, barbiturates, carbamazepine, or phenytoin
- Start or stopping of birth control pill use in the 12 weeks before study entry
- Pregnant or nursing females

Washout Periods

- Topical acne medications - 14 days
- Cosmetic or surgical procedures - 15 days
- Systemic antibiotics - 30 days
- Estrogens or steroids - 12 weeks
- Oral retinoics - 12 months

Study Design

- Open-label, single-group, prospective pilot study (IRB-approved protocol)
- 12-week duration with visits at baseline and weeks 4, 8, and 12

Treatment Regimen

- 5% benzoyl peroxide/1% clindamycin gel (a ready-to-dispense formulation containing two emollients) applied in the morning
- Tazarotene 0.1% cream applied in the evening
- Oral minocycline 100mg capsules taken BID (once in the morning, once in the evening)
  - ► Minocycline dose could be reduced at the discretion of the investigator
- A soap free cleanser was provided for use prior to applying the study medication
- A hydrating cream was provided for use as needed during the study

Efficacy Measures

- Primary efficacy variable
  - ► Investigator assessment of global response to treatment (Table 1)
- Secondary efficacy variables
  - ► Inflammatory lesion count (papules plus pustules), non-inflammatory lesion count, and nodule/cyst count
  - ► Overall disease severity (Table 2)

Table 1. Investigator grading of global response to treatment

Score	Grade	Definition
0	Completely cleared	No signs or symptoms of disease
1	Almost cleared	Approximately 80% (high-point), very significant clearance, only traces of disease remaining
2	Marked improvement	Approximately 75% improvement, significant improvement with some disease remaining
3	Moderate improvement	Approximately 50% improvement, between mild and marked improvement
4	Mild improvement	Approximately 25% improvement, some improvement, but significant disease remains
5	No change	No noticeable improvement from baseline assessment
6	Exacerbation	Worsening of signs and symptoms of disease

Table 2. Overall disease severity

Score	Definition
0	None – clear, no inflammatory lesions
1	Almost clear/minimal, with very few or no inflammatory lesions present
2	Mild severe/acne, with some small inflammatory lesions present, minimal erythema
3	Considerable with an increasing number of inflammatory lesions compared to score 2
4	Moderately severe/acne, a moderate number of small inflammatory lesions extending over a wider area of the facial erythema & increasing
5	Considerable, an increasing number of inflammatory lesions compared to score 4, with some larger inflamed lesions
6	Severe, numerous comedones, papules and pustules with larger inflamed lesions extending over much of the face; erythema may be pronounced

Table 3. Investigator grading of peeling, erythema, dryness, and perception of oiliness

Score	Grade	Definition
0	None	Normal
1	Trace	Mild and localized
2	Mild	Mild and diffuse
3	Moderate	Moderate and diffuse
4	Marked	Moderate and severe
5	Severe	Prominent and severe

Table 4. Subject grading of burning and pruritus

Score	Grade	Definition
0	None	Normal, not dysesthetic
1	Trace	An awareness, but not dysesthetic and no intervention required
2	Mild	Noticeable dysesthetic causing intermittent awareness
3	Moderate	Noticeable dysesthetic causing continuous awareness
4	Marked	Definite dysesthetic causing continuous awareness that interferes occasionally with normal daily activities
5	Severe	Definite, continuous dysesthetic that interferes with normal daily activities

- Investigator grading of peeling, erythema, dryness, and perception of oiliness (Table 3)
- Subject grading of burning and pruritus (Table 4)

Safety Measures

- Reporting of adverse events

Statistical Analysis

- A *P* value of ≤0.05 was considered statistically significant.
- Primary efficacy outcome was the proportion of "Responders" as measured by global response to treatment (a score of 2 or better).
- Efficacy variables assessed using paired T-tests and Wilcoxon Signed-Rank Tests.

RESULTS

Subjects

- 14 subjects (7 males and 7 females) enrolled in the study; 12 subjects completed at the time of data analysis (1 subject withdrew at Visit 1 and 1 subject completed up to week 8 at time of data analysis).
- Subjects were predominantly White (79%) and Asian (14%) with a mean age of 16.5 years.

Efficacy

- There was a significant decrease ($p<0.05$) in the inflammatory lesion count, non-inflammatory lesion count, and nodule/cyst count at weeks 4, 8, and 12 compared to baseline (Figures 1 and 2).
- There was a significant mean percent reduction from baseline in:
  - ► Inflammatory lesion count (72% at week 12; $p<.0001$) (Figure 3)
  - ► Non-inflammatory lesion count (63% at week 12; $p<.0001$) (Figure 3)
  - ► Nodule/cyst count (95% at week 12; $p<.01$).

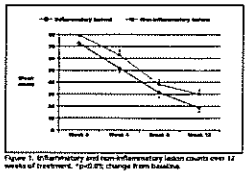

Figure 1. Inflammatory and non-inflammatory lesion counts over 12 weeks of treatment. *p<0.05; change from baseline.

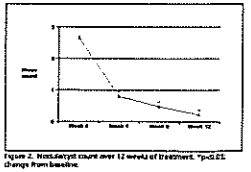

Figure 2. Nodule/cyst count over 12 weeks of treatment. *p<0.05; change from baseline.

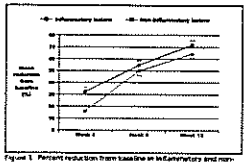

Figure 3. Percent reduction from baseline in inflammatory and non-inflammatory lesion counts over 12 weeks of treatment. *p<0.001; **p<0.0001; percent reduction from baseline.

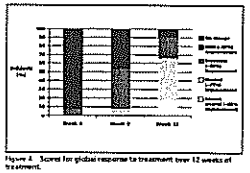

Figure 4. Scores for global response to treatment over 12 weeks of treatment.

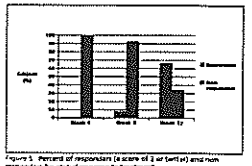

Figure 5. Percent of responders (a score of 2 or better) and non-responders for global response to treatment.

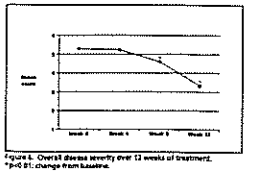

Figure 6. Overall disease severity over 12 weeks of treatment. *p<0.01; change from baseline.

Figure 7. Improvement in severe acne vulgaris after combination therapy with 5% benzoyl peroxide/1% clindamycin gel, tazarotene 0.1% cream, and oral minocycline.

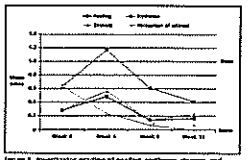

Figure 8. Investigator grading of peeling, erythema, dryness, and perception of oiliness over 12 weeks of treatment. *p<0.05; significant change from baseline for perception of oiliness at weeks 8 and 12

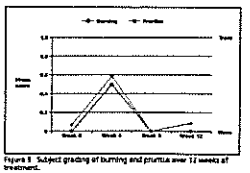

Figure 9. Subject grading of burning and pruritus over 12 weeks of treatment.

- At week 12, 67% of subjects qualified as responders (at least marked improvement, i.e. a score of 2 or better) for global response to treatment (Figures 4 and 5).
- There was a significant improvement ($p<0.01$) in overall disease severity at weeks 8 and 12 compared to baseline (Figures 6 and 7).
- There was a significant improvement ($p<0.05$) from baseline for investigator grading of perception of oiliness at weeks 8 and 12 (Figure 8).
- There were no significant changes from baseline for subject grading of burning and pruritus (Figure 9).

Safety

- 5 subjects (38%) reported 7 mild adverse events (fever, depression, headaches, sore throat, nausea, stomach ache, and upset stomach).
- There were no adverse events related to treatment.

CONCLUSION

- Given the anticipated restrictions for systemic isotretinoin, it is useful to evaluate the potential of other anti-acne agents that could play a role in the treatment of severe acne vulgaris. Combination therapy is likely to offer the greatest efficacy.
- The results of this study suggest that combination therapy using 5% benzoyl peroxide/1% clindamycin gel, tazarotene 0.1% cream, and oral minocycline may offer good efficacy and safety in the treatment of severe acne vulgaris.
- At week 12, 67% of subjects had a score of "marked improvement" or better and 92% of subjects had a score of "moderate improvement" or better for global response to treatment.
- The inflammatory lesion count, non-inflammatory lesion count, and nodule/cyst count decreased throughout the 12 weeks of treatment.
- Overall disease severity was significantly improved at weeks 8 and 12 compared to baseline.
- Perception of oiliness, as graded by the investigators, was also significantly lower at weeks 8 and 12 compared to baseline.
- Based on historical data, the efficacy achievable with this combination treatment regimen approaches that achievable with systemic isotretinoin—but with fewer adverse events.

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DISCLOSURE

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