A Randomized, Double-Blind, Placebo-Controlled, Pilot Study to Assess the Efficacy and Safety of Clindamycin 1.2% and Tretinoin 0.025% Combination Gel for the Treatment of Acne Rosacea Over 12 Weeks

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ABSTRACT

Background: Papulopustular acne rosacea is a chronic inflammatory condition which can be difficult to treat. Many patients are unwilling to use systemic medications, and single topical agents alone may not address all the symptoms of rosacea. A combination topical clindamycin phosphate 1.2% and tretinoin 0.025% gel is efficacious for acne vulgaris, and may be helpful for rosacea, since acne vulgaris and rosacea shares many similar clinical and histologic features.

Objective: To assess the preliminary efficacy and safety of a combination gel consisting of clindamycin phosphate 1.2% and tretinoin 0.025% on papulopustular rosacea after 12 weeks of usage.

Methods: Randomized, double-blind, placebo controlled two site study of 79 participants with moderate to severe papulopustular acne rosacea using both physician and subjects' validated assessment tools. Primary endpoint consisted of statistically significant reduction in absolute papule or pustule count after 12 weeks of usage.

Results: There was no significant difference in papule/pustule count between placebo and treated groups after 12 weeks (P=0.10). However, there was nearly significant improvement in physicians' assessments of the telangiectasia component of rosacea (P=0.06) and erythematotelangiectatic rosacea subtype (P=0.05) in treated versus placebo group after 12 weeks. The only significant adverse event different was facial scaling, which was significantly increased in treated group (P=0.01), but this did not result in discontinuation of study drug.

Conclusions: A combination gel of clindamycin phosphate 1.2% and tretinoin 0.025% may improve the telangiectatic component of rosacea and appears to better treat the erythemotelangiectatic subtype of rosacea rather than papulopustular subtype. Our preliminary study suggests that future studies with much larger sample size might confirm our findings. Clinical Trials: NCT00823901.

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INTRODUCTION

Acne rosacea is a common chronic disease affecting up to 10% of fair-skinned individuals.[1] It is characterized by inflammation and vascular abnormalities of primarily the facial skin and ocular surface. It can encompass various combinations of cutaneous signs including erythema, telangiectasia, papules, pustules, edema, ocular lesions and rhinophyma. The exact etiology of cutaneous rosacea is unknown, but is thought to be characterised by persistent vasodilatation, increased vascular permeability and vascular hyper-reactivity of the microcirculation of the central part of the face. Perifollicular dermal inflammation, elastin and collagen degeneration, and vascular dilatation are important findings in its histopathology.[2]

The National Rosacea Society Expert Committee proposed a classification and staging system. This system defines four subtypes: erythemato-telangiectatic, papulopustular, phymatous, and ocular.[3] Although rosacea is not clearly of infectious origin, oral and topical antibiotics (such as tetracyclines, macrolides, metronidazole) are effective in treating the papulopustular subtype of rosacea. More recently, submicrobial doses of doxycycline have been shown to improve rosacea through its putative anti-inflammatory properties.[4]

In recalcitrant cases where antibiotics have failed or are only partially successful, oral or topical tretinoin therapy may be ef-

fective.[5,6] In human beings and animal models, chronic therapy with topical tretinoin promotes remodeling of the collagen in the papillary and reticular dermis and decreases dermal inflammation.[7,8] Retinoids also produce inhibitory effects on vascular endothelial growth factor production by cultured human skin keratinocytes.[9] In fact, some studies have demonstrated positive effects of topical retinoids in the treatment of rosacea, not only in the papulopustular component but also in erythema.[6] The clinical response to topical retinoids appears to be delayed, starting usually in 1-2 months of therapy. Retinoids also produce inhibitory effects on vascular endothelial growth factor production by cultured human skin keratinocytes.[9]

Clindamycin lotion has been compared favorably to oral tetracycline therapy in an investigator-blinded 12-week trial of 43 patients with acne vulgaris.[10,11] Topical clindamycin (twice daily) produced clearance that was similar to oral tetracycline and is more effective than tetracycline for the eradication of pustules.[10,11] The combination of clindamycin phosphate 1.2% and tretinoin 0.025% gel (CT gel) has been FDA approved for acne vulgaris. Acne vulgaris shares similarities with acne rosacea in that both consist of follicle-based inflammation clinically and histologically and therefore it might be predicted that papulopustular subtype might respond well to CT gel. In this study, we explore the possibility that CT gel may improve acne rosacea.

Objective

The objective of this study was to assess the safety and efficacy of CT versus placebo gel in subjects with papulopustular rosacea. The primary endpoint was the absolute change in inflammatory lesion counts (papules and pustules) from baseline to week 12 (end of treatment) as assessed by both physician and participant, both of whom are blinded to treatment. Secondary endpoints include percentage of participants in treated versus placebo groups with improvement in at least one symptom category after 12 weeks. Side effect incidence was compared as well between treated and placebo groups.

METHODS

Study Population and Procedures

A summary of the study design is shown in Figure 1. This was a randomized, double blind, placebo-controlled study at two academic centers, which consisted of one screening visit and four study visits. This study was conducted according to Declaration of Helsinki principles registered on www.clinicaltrials.gov. Following Institutional Review Board approval at both Massachusetts General Hospital and Stanford Hospital and Clinics, participants were recruited from advertisements in local newspapers, posters, and the internet. Following a preliminary telephone screen, potential study subjects underwent the informed consent process prior to all study procedures. Inclusion and exclusion criteria were reviewed, medical histories obtained, and their skin was examined by a board-certified dermatologist. Inclusion criteria included: ≥18 years of age, clinical diagnosis of papulopustular facial rosacea, 4 to 50 facial inflammatory lesions (papules plus pustules). The following exclusion criteria were used: acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne, etc.) or severe acne requiring systemic treatment; history of regional enteritis or inflammatory bowel disease; use of topical rosacea treatments in the past two weeks; use of systemic antibiotics in the past four weeks; use of systemic retinoids within the past three months; use of laser or light-based rosacea treatments within the past two months; concomitant use of medications that are reported to exacerbate rosacea, such as topical and systemic steroids; current drug or alcohol abuse; other dermatologic conditions that require the use of interfering topical or systemic therapy or that might interfere with study assessments such as, but not limited to, atopic dermatitis, perioral dermatitis or acne vulgaris; pregnant or planning a pregnancy; use of any investigational therapy within the past four weeks; known hypersensitivity or previous allergic reaction to clindamycin or retinoids.

Qualifying subjects were randomized via a computerized random number generator to into two nearly equal populations and selected to receive either CT or placebo gel. The research staff member who randomized the study population was not involved with any study assessments. The CT gel and placebo gels were indistinguishable on visual inspection with respect to color, consistency and odor. The study subjects were instructed to apply the gel once daily for 12 weeks, and were given diaries to record usage and side effects. The weights of the gel tubes were taken at each visit to confirm compliance with CT and placebo gel usage.

Sample size was determined based on prior studies in the medical literature, with study subjects having a baseline papule or pustule count between 15 to 17 lesions. We estimated the CT group would experience a 50% improvement and that the placebo group would show a 35% improvement. Using a standard deviation of 3.5 lesions, a power of 80% and a 2-tailed alpha of 0.5, a sample size of 35 patients per group was needed to achieve statistical significance. To allow for a 15% to 20% dropout rate, 41 to 43 subjects for each group was needed. We used a modified intention-to-treat analysis (mITT) defined as the population that completed at least one follow-up visit defined as week 2, 6, or 12.

In addition to the screening visit, study subjects participated in four follow-up visits: baseline (day 1), interim assessments (at weeks 2, 6), and final assessments (at week 12). In all four visits, physician and patient rosacea assessment instruments derived from the National Rosacea Scoring System[12,13] were administered. Optional photographs were taken.

Primary endpoints in the study included a statistically significant decrease in absolute count of papules/pustules on the face at week 12 compared to baseline, as well as percent decreased in papule/pustule count on the face at week 12 compared to

FIGURE 1. Study flowchart. This study is limited by relatively small number of subjects. In addition, overall assessment of acne rosacea severity as determined by subjects' self-assessment was not performed, an inadvertent omission from the protocol.

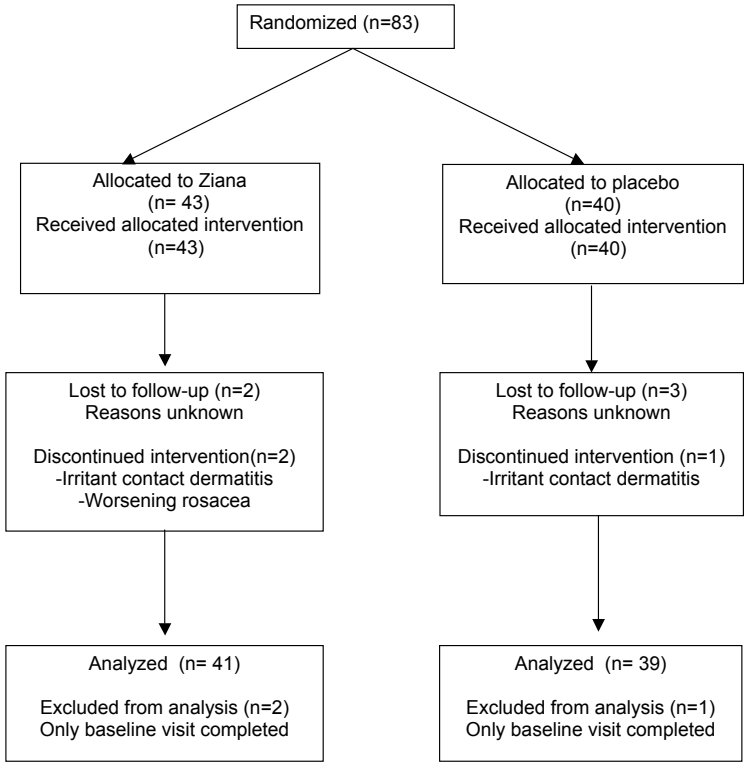

TABLE 1.

Baseline Characteristics of Study Subjects

Characteristic	CT gel n=41	Placebo n=39	*P*-value
Age – mean (SD) in years	53.2 (13.6)	51.2 (14.0)	0.524
Male – n (%)	14 (34.1)	9 (23.1)	0.32*
No. of papules and pustules – mean (SD)	14.3 (9.5)	18.7 (14.1)	0.095

* Fisher Exact test (two-tail probability).

baseline. Secondary endpoints consisted of statistically significant improvement at week 12 in clinical features of rosacea such as flushing, erythema, papules and pustules, telangiectasia, burning or stinging, plaques, dry appearance, edema, ocular symptoms, peripheral location, phymatous changes. Additional secondary endpoints included improvements in physician global assessments regarding the following rosacea subtypes: erythematotelangiectatic, papulopustular, phymatous; improvements in subject self-assessments; statistically significant improvements in standard tolerability features of scaling, dryness and erythema; and statistically significant differences in the nature and severity of adverse events between CT and placebo groups at week 12.

RESULTS

Eighty-three subjects enrolled in the study, with 43 subjects allocated to CT group and 40 to placebo group (Figure 1). The average age of the study subjects was in the early 50s and about two-thirds of the subjects were female. As indicated in Table 1, there were no statistically significant differences at baseline between the CT and placebo groups with regard to age and sex distribution. Similarly, there was no difference in rosacea disease severity as measured by papule/pustule count at baseline.

Of the 83 study subjects enrolled, 73 subjects (88%) completed all study visits. In the CT group there was one early termination due to irritation from CT gel, and one due to worsening rosacea. In the placebo group, one subject withdrew participation because of irritant dermatitis. One subject in the CT group was lost to follow-up, while two subjects in the placebo group were lost to follow-up, for unknown reasons. Three patients were excluded from the mITT analysis because they did not complete at least one follow-up visit.

Primary and Secondary Endpoints

As indicated in Table 2, there were no significant differences in absolute papule/pustule count after 12 weeks in either the CT (P=0.63) or placebo groups (P=0.15). The percentage of sub-

TABLE 2.

Papule and Pustule Count at Baseline and Week 12				
Group	**Baseline**	**Week 12**	**Mean difference in count**	***P*-value**
CT – mean (SD)	14.3 (9.5)	14.4 (13.2)	0.83 (10.84)	0.63
Placebo – mean (SD)	18.7 (14.1)	15.9 (11.6)	-3.13 (13.28)	0.15

Week 12 across-group comparisons	P-value
Mean difference in count: CT vs. placebo at wk 12	0.15
Mean % improvement: CT vs. placebo at wk 12	0.20

TABLE 3.

Percentage With Improvement in Physician Assessments of Primary Features of Rosacea at Week 12.			
Primary Features	**CT Group**	**Placebo Group**	***P*-value***
Flushing	10 (26%)	11 (28%)	0.80
Erythema	11 (28%)	6 (15%)	0.27
Papules and pustules	7 (18%)	6 (15%)	0.77
Telangiectasia	13 (33%)	5 (13%)	0.06
Burning or stinging	10 (27%)	17 (49%)	0.09
Plaques	3 (8%)	3 (8%)	1.00
Dry appearance	10 (25%)	14 (36%)	0.33
Edema	0 (0)	6 (16%)	0.03
Ocular	8 (21%)	9 (24%)	0.79
Peripheral location	2 (6%)	3 (9%)	1.00
Phymatous changes	1 (3%)	6(15%)	0.11
Erythematotelangiectatic	12 (30%)	4 (10%)	0.05
Papulopustular	8 (20%)	8 (21%)	1.00
Phymatous	6 (15%)	7 (18%)	0.77
Ocular	6 (15%)	5 (13%)	1.00
Physician Global Assessment	10 (25%)	7 (19%)	0.58

*Fisher Exact test (two-tail probability).
Shaded numbers indicate statistically significant or nearly significant improvement.

jects with decreased papule/pustule count was not statistically significant between the treated and the placebo group at week 12. The across-group comparisons of mean change in papule/pustule count after 12 weeks for CT and placebo were non-significant (*P*=0.15). The across-group comparisons of percentage of subjects with improvement after 12 weeks between CT and placebo were non-significant (*P*=0.20).

Table 3 depicts the results of physician-assessed primary features of rosacea after 12 weeks. There was a trend towards significance in CT versus placebo group with respect to improvements in telangiectasia (*P*=0.06), with odds ratio (OR) 3.157 and 95% confidence interval [1.003–9.934], and erythematotelangiectatic subtype of rosacea (*P*=0.05), with OR 3.6207 and 95% confidence interval [1.054-12.437]. Figure 2 depicts a subject with reduction of telangiectasia and erythematotelangiectatic rosacea subtype severity after 12 weeks. Neither telangiectasia nor erythematotelangiectasia severity was significantly different at baseline between the CT and placebo groups. One unexpected significant finding was that placebo subjects showed statistically significant improvements in edema (*P*=0.03) at 12 weeks, while CT group did not. None of the other physician-assessed clinical features of rosacea reached statistical significance.

Table 4 shows the results of subjects' self-assessments of rosacea severity. In particular, this table indicates that the CT group showed more improvement at 12 weeks on almost all param-

FIGURE 2. Example of a subject with acne rosacea at **a)** baseline and after 12 weeks of treatment **b)** demonstrating decreased erythematotelangiectatic rosacea on the face.

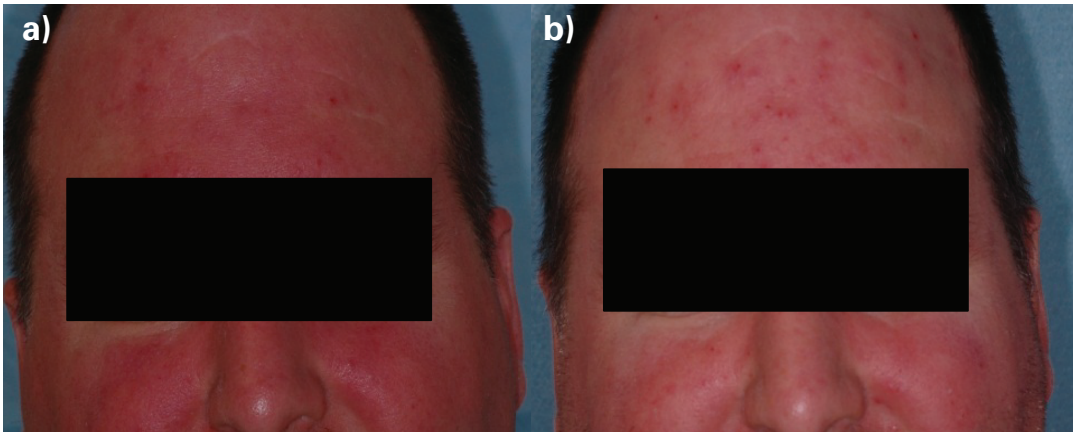

TABLE 4.

Study Subject Self-Assessment of Improvement at Week 12.

Survey Item:	CT	Placebo	*P*-value*
1. I worry that my rosacea may be serious.	16 (39%)	13 (33%)	0.65
2. My rosacea burns or stings.	9 (22%)	11 (28%)	0.61
3. I worry about getting scars from my rosacea.	19 (46%)	14 (36%)	0.37
4. I worry that my rosacea may get worse.	18 (43%)	14 (36%)	0.65
5. I worry about side effects from rosacea medications.	12 (29%)	13 (33%)	0.81
6. My rosacea is irritated.	16 (39%)	13 (33%)	0.66
7. I am embarrassed by my rosacea.	18 (44%)	14 (36%)	0.5
8. I am frustrated by my rosacea.	22 (54%)	13 (33%)	0.08
9. My rosacea makes my skin sensitive.	14 (34%)	11 (28%)	0.63
10. I am annoyed by my rosacea.	15 (38%)	13 (33%)	0.81
11. I am bothered by the appearance of my skin (redness, blotchiness).	18 (44%)	12 (31%)	0.255
12. My rosacea makes me feel self-conscious.	12 (29%)	11 (28%)	1.0
13. I try to cover up my rosacea (with make-up).	10 (24%)	7 (18%)	0.59
14. I am bothered by persistence/reoccurrence of my rosacea.	19 (46%)	12 (31%)	0.17
15. I avoid certain foods or drinks because of my rosacea.	11 (27%)	7 (18%)	0.43
16. My skin feels bumpy (uneven, not smooth, irregular).	18 (44%)	16 (41%)	0.82
17. My skin flushes.	20 (49%)	14 (36%)	0.27
18. My skin gets irritated easily (cosmetics, aftershaves, cleansers).	15 (37%)	15 (38%)	1.00
19. My eyes bother me (feel dry or gritty).	14 (34%)	12 (31%)	0.81
20. I think about my rosacea.	14 (34%)	10 (26%)	0.47
21. I avoid certain environments (heat, humidity, cold) because of my rosacea.	13 (32%)	9 (23%)	0.46

* Fisher Exact test (two-tail probability)

TABLE 5.

Tolerability: Physician-Assessed Severity at Week 12.

Scaling	CT	Placebo	P-value*
Improved	11 (29%)	16 (43%)	0.234
Worsened	10 (26%)	4 (11%)	0.137
Dryness	18 (43%)	14 (36%)	0.65
Improved	14 (37%)	11 (30%)	0.626
Worsened	8 (21%)	5 (14%)	0.544
Erythema	9 (22%)	11 (28%)	0.61
Improved	15 (38%)	12 (32%)	0.635
Worsened	10 (26%)	7 (18%)	0.584

* Fisher Exact test (two-tail probability)

TABLE 6.

Adverse Events (AEs)

Adverse Event	CT	Placebo	*p*-value
Worsening rosacea	7 (17.5%)	4 (25.0%)	0.35
Facial scaling	6 (15%)	0 (0%)	0.01
Dry skin on face	5 (22.7%)	2 (12.5%)	0.26
Redness on facial skin	4 (18.1%)	2 (12.5)	0.43
Facial burning	2 (9%)	0 (0%)	0.24
Itching facial skin	3 (7.5%)	2 (12.5)	0.67
Increased blood pressure	2 (9%)	0 (0%)	0.24
Irritated Facial Skin	2 (5%)	1 (2.5%)	0.62

*Fisher's Exact test (two-tailed)

eters compared to the placebo group. However, none of the individual survey items reached statistical significance in the CT compared with placebo group.

Tolerability and Safety

As indicated in Table 5, CT gel was well-tolerated by subjects in the CT group. Scaling, dryness and erythema were not significantly worse or better in the CT versus placebo group at week 12.

There were no serious adverse events in either the CT or placebo groups. Table 6 shows adverse events that were observed more than once in the CT or placebo groups. None were statistically significant between CT or placebo groups except for facial scaling, which was increased in the CT group, as would be expected since the CT gel included tretinoin.

CONCLUSIONS

CT gel may reduce the visible appearance of telangiectasias of rosacea, a finding that clearly merits further study through studies with larger sample size. If confirmed, this finding would fill a critical need in the topical armamentarium for rosacea. For instance, a 2009 Cochrane Collaboration review of topical interventions for rosacea showed only one randomized placebo controlled trial with improvements in telangiectasia.[14] That study utilized 1% metronidazole cream with SPF 15 sunscreen.[15] Per the www.clinicaltrials.gov website, studies using topical alpha-1 agonists for erythema and/or telangiectatic component of facial rosacea are ongoing.

We had expected that CT gel would improve the papulopustular component of rosacea, given its proven efficacy to eradicate papules in acne vulgaris. It may be possible that as the erythematotelangiectatic subtype of rosacea for some subjects improved, their papules could be more readily detected.

> "CT gel may reduce the visible appearance of telangiectasias of rosacea, a finding that clearly merits further study through studies with larger sample size."

Although rosacea patients are anecdotally thought to possess sensitivity to topical agents such as tretinoin, CT gel was well tolerated compared to the placebo gel. While CT gel did lead to more patient reports of facial scaling than placebo gel during the course of the study, this side effect was not reported more often as the reason for discontinuing the study. Furthermore, there were no differences in scaling that could be detected by the physician assessment at 12 weeks between the two groups.

Finally, the mechanism by which CT gel might contribute to reduced appearance of telangiectasias merits further study. It is possible that telangiectasias are less visible because clindamycin is an anti-microbial agent that leads to decreased inflammation. Another mechanism might be that tretinoin decreases the visibility of telangiectasias by inducing collagen formation in the upper dermis or via proliferation of keratinocytes,[7,8] both of which might obscure the appearance of telangiectasias.

DISCLOSURES

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