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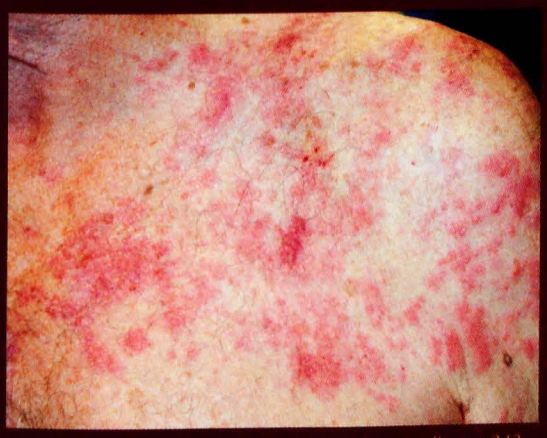

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VARIOUS TOPICS

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Use of Dapsone 5% Gel as Maintenance Treatment of Acne Vulgaris Following Completion of Oral Doxycycline and Dapsone 5% Gel Combination Treatment

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ABSTRACT

Background: Acne vulgaris is a common, chronic skin disease that requires long-term therapy. Oral antibiotics are a mainstay of treatment, but extended use is associated with the development of bacterial resistance. Topical therapies are often combined with oral antibiotics to achieve an initial improvement, after which the oral agents may be discontinued and the topical therapy used as maintenance.
Objective: To assess the safety and efficacy of combination therapy with dapsone 5% gel with oral doxycycline hyclate 100mg, followed by monotherapy with dapsone 5% gel in improving and maintaining response in patients with moderate to severe acne.
Methods: In this open-label study, all patients applied dapsone 5% gel twice daily along with doxycycline hyclate 100mg once daily for 12 weeks. Subjects who achieved a qualifying improvement at week 12 continued to the second phase of the study in which they applied only dapsone 5% gel twice daily for maintenance therapy of 12 more weeks. Subjects were evaluated for safety and efficacy at weeks 4, 8, 12, 16, 20, and 24.
Results: All subjects (n=30) in the initial phase qualified to enter the maintenance phase. 82% of participants maintained their treatment response (Investigator's Global Assessment score) at week 24. The regimen was safe and well tolerated.
Conclusions: The combination oral doxycycline hyclate 100 mg with topical dapsone 5% gel twice daily is an effective and well-tolerated regimen to treat moderate to severe acne vulgaris. After discontinuation of doxycycline, topical dapsone 5% gel is effective at maintaining a therapeutic response. These data suggest that topical dapsone 5% gel can be used effectively for long-term acne maintenance treatment without the risk of developing antibiotic resistance.

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INTRODUCTION

In the real world, acne is a chronic disease that requires maintenance treatment beyond the 12-week evaluation period used in most clinical trials. Combination therapy, using different drugs with complimentary mechanisms of action is considered standard of care in treating acne. While oral antibiotics are commonly used initially to control moderate to severe acne, they should not be used as long-term maintenance because of the risk of promoting bacterial resistance. Topical retinoids have traditionally been the preferred option for maintenance therapy.[1,2] Topical dapsone 5% gel has been approved for treatment of acne vulgaris since 2005. It has been used for acne vulgaris with proven efficacy and safety during post marketing in addition to a long-term safety study.[3] However, there is a paucity of data evaluating topical dapsone 5% gel as maintenance following a successful course of antibiotics.

The current study investigated whether dapsone 5% gel could be

METHODS

Study Design

Thirty two subjects with moderate to severe facial acne vulgaris were enrolled into this two-site, open-label, pilot study. Subjects entered into a 12-week initial treatment phase followed by a 12-week maintenance phase for qualifying patient. In the initial treatment phase, patients received doxycycline hyclate 100 mg once daily in combination with dapsone 5% gel twice daily. In the maintenance phase, the oral antibiotic was discontinued and patients applied dapsone 5% gel twice daily as monotherapy. Participants had 7 study visits; baseline and weeks 4, 8, 12, 16, 20, and 24. At the week 12 visit, subjects who achieved a qualifying treatment response, moved on to the maintenance phase. Subjects who did not achieve a qualifying treatment response at week 12 were discontinued from the study.

The sample size of 32 subjects was chosen based on the assumption that 66% of subjects (approximately 20 subjects)

Inclusion Criteria

Male and female patients at least 12 years old of any race were eligible for enrollment. Participants had facial acne vulgaris judged to be moderate or severe (3-4 on the Investigator's Global Assessment (IGA) scale), with 10-50 inflammatory lesions (eg, papules, pustules) and 10-100 non-inflammatory lesions (eg, open, closed comedones). Female subjects of childbearing potential had to have a negative urine pregnancy test result at baseline and were required to practice a reliable method of contraception throughout the study.

Exclusion Criteria

Patients were excluded from participation in the study if they were female and pregnant, breast-feeding, or of childbearing potential but not practicing a reliable method of birth control. Patients were also excluded if they had an allergy to any component of the dapsone 5% gel, lincomycin, tetracycline, or sulfites. Standard wash-out periods of 14 days for topical acne medications, 30 days for oral antibiotics or other investigational drugs, and 6 months for oral retinoids were used. Patients with a history of clinically significant anemia, hemolysis, or glucose-6-phosphate dehydrogenase (G6PD) deficiency, or enteritis (including regional enteritis, ulcerative colitis, pseudomembranous colitis, or antibiotic-associated colitis) were prohibited from participating.

Treatment Regimen

During the initial treatment phase, patients applied dapsone 5% gel to the face twice daily in combination with once daily doxycycline hyclate 100 mg once a day in the morning. Patients were instructed to use a pea-sized amount of dapsone 5% gel after washing their face with a gentle cleanser. All patients were given the same moisturizer and gentle cleanser. At week 12, subjects' global response to therapy was evaluated. Those who achieved an IGA score of at least mild (IGA 0, 1, or 2) moved on to the second phase of the study. During the maintenance phase, subjects discontinued doxycycline therapy and applied dapsone 5% gel twice daily as monotherapy for an additional 12 weeks. Subjects were evaluated to assess whether improvement would remain with topical monotherapy.

Randomization

This was an open-label investigation, in which all subjects received active treatment. Patients who achieved an IGA score of clear, almost clear, or mild were advanced into the maintenance phase of the study, in which all patients again received active treatment.

Main Outcome Measures

The primary efficacy outcome was the IGA score, a 6-point scale where 0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe, 5=very severe (Table 1). Secondary outcomes included evaluation of medication tolerability, including erythema, dryness, peeling, and oiliness on a five grade scale (Table 2). Finally, any application site reactions such as stinging and burning were also assessed using a 6-point severity scale (Table 3).

TABLE 1.

IGA-Investigator Global Assessment

0 = Clear Skin	Clear Skin; no inflammatory or non-inflammatory lesions
1 = Almost Clear	Almost clear; rare non-inflammatory lesions with no more than one small inflammatory lesion
2 = Mild Severity	Mild severity; greater than Grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3 = Moderate Severity	Moderate severity; greater than Grade 2; some to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4 = Severe	Severe; greater than Grade 3; some to many non-inflammatory and inflammatory lesions, but no more than a few nodular lesions
5 = Very Severe	Very Severe; greater than Grade 4; many non-inflammatory and/or inflammatory lesions with some or many nodular lesions

Statistical Analysis

Statistical analyses were conducted on the intent-to-treat population, ie, all enrolled subjects were included. All statistical tests were 2-sided and interpreted at a 5% significance level.

RESULTS

Patients

A total of 32 patients with moderate to severe facial acne were enrolled in two United States investigational research centers. The majority of patients (62.5%) were female. The mean and median ages of subjects were 24.8 and 21.5 years old, respectively. The youngest patient enrolled was 12.8 years old and the oldest was 48.7 years old. The majority (71.9%) of patients were Caucasian. The full subject demographic information is summarized in Table 4.

Of the 32 patients, 24 (75%) completed the initial treatment phase. All (100%) of the patients who completed the initial phase qualified to move into the maintenance phase of the study. Of the 24 patients, 22 completed the maintenance phase.

TABLE 2.

Tolerability Scores

0 = Absent	No redness	None	Smooth	Normal
1 = Trace	Faint red or pink coloration, barely perceptible	Barely perceptible dryness by palpation with no accentuation of skin markings, skin desquamation (flakes) or fissure formation	Fine peeling, barely perceptible	Mild and localized
2 = Mild	Light red or pink coloration	Easily perceptible dryness by palpation with accentuation of skin markings but no skin desquamation (flakes) or fissure formation	Slight peeling	Mild and diffuse
3 = Moderate	Medium red coloration	Easily noted dryness with accentuation of skin markings and skin desquamation (small flakes) but no fissure formation	Definitely noticeable peeling	Moderate and diffuse
4 = Severe	Beet red coloration	Easily noted dryness with accentuation of skin markings, skin desquamation (large flakes) and/or fissure formation	Extensive peeling	Prominent and dense

maintenance phase (week 24) compared to the end of initial treatment phase (week 12). The success was defined as an IGA score of 0, 1, or 2. This was first assessed after the initial phase at week 12 compared to baseline, then again after the maintenance phase at week 24 compared to week 12. Combination therapy with doxycycline 100 mg daily with topical dapsone gel 5% twice daily resulted in a treatment response in 30% of subjects by week 4, 67% of subjects by week 8, and 100% of subjects at week 12. 100% of subjects qualified to enter the maintenance phase, during which the doxycycline was discontinued and subjects were treated with topical dapsone gel 5% twice daily as monotherapy. 78.3%, 87%, and 82% of subjects maintained their treatment response at weeks 16 (4 weeks post-phase 1), 20 (8 weeks post-phase 1), and 24 (12 weeks post-phase 1), respectively. At week 24, topical dapsone 5% gel twice daily did not maintain therapeutic response in only a minority (18%) of patients.

TABLE 3.

Stinging and Burning Severity Scale

0 = Absent	Normal, no discomfort
1 = Trace	An awareness, but no discomfort and no intervention required
2 = Mild	Noticeable discomfort causing intermittent awareness
3 = Moderate	Noticeable discomfort causing continuous awareness
4 = Marked	Definite discomfort causing continuous

Inflammatory Lesion Count

Compared to baseline, combination therapy resulted in a 39.8% and 54.7% mean reduction in inflammatory lesions at weeks 4 and 8. By week 12, there was a 79.4% mean reduction in inflammatory lesions, which was maintained throughout the second phase of the study. After discontinuation of doxycycline, twice daily application of dapsone 5% gel provided a sustained reduction in inflammatory lesions; at weeks 16, 20, and 24, there was a mean percent reduction of 80.5%, 78%, and 77.8% compared to baseline. All inflammatory lesion count reductions were statistically significant compared to baseline (P <0.0001). In addition, there were no statistical differences in the overall mean percent change in inflammatory lesions at any point during the maintenance phase compared to week 12.

Non-inflammatory Lesion Count

Statistically significant decreases in the mean percent reduction of non-inflammatory lesion counts were achieved throughout the initial study phase compared to baseline (P<0.0001). There was a 32.2%, 60.6%, and 75.6% mean reduction in non-inflammatory lesions at weeks 4, 8, and 12. The mean percent reduction in non-inflammatory lesions was sustained with dapsone 5% gel monotherapy twice daily. At weeks 16, 20, and 24, there was a 77.8%, 81.5%, and 84.7% decrease compared to baseline (P <0.0001). In addition, there was a statistically significant reduction in non-inflammatory lesions at week 24 compared to week 12 (52.6% mean percent reduction, P =0.038).

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