A Novel Gel Formulation of Clindamycin Phosphate–Tretinoin Is Not Associated With Acne Flaring

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Concern exists about using topical retinoids on patients with inflammatory acne lesions, fearing that a flare in inflammation will occur. In 3 multicenter, double-blind, randomized, phase 3 trials of a clindamycin phosphate 1.2%–tretinoin 0.025% gel (CLIN/RA), clinical evaluations after 2 weeks of treatment determined if flaring occurred in participants treated with tretinoin gel 0.025% (RA) monotherapy, and the difference in inflammation when treated with the combination formulation. Flaring was assessed as an increase in inflammatory lesions of 10% or greater or 20% or greater versus baseline. Most participants experienced improvement in lesions across treatment groups. Participants with mild acne at baseline treated with RA monotherapy had significantly higher rates of flaring compared with participants treated with vehicle gel (VEH)(P<.001). Treatment with CLIN/RA or clindamycin phosphate gel 1.2% (CLIN) monotherapy resulted in significantly lower rates of flaring than RA or VEH (P<.001 for all). Participants with moderate to severe acne showed no signs of RA-induced flaring. In each comparison, the CLIN/RA combination showed the lowest percentage of increased inflammatory lesions. These results indicate that RA-induced flaring may occur with mild inflammation; combining RA with CLIN prevents this flaring. Participants with moderate to severe inflammatory acne did not show an increase in inflammatory lesions compared with participants treated with VEH. Lack of flaring may result from either the novel vehicle formulation or the anti-inflammatory effects of CLIN.

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Topical retinoids comprise one of the major classes of drugs used for the treatment of acne. The primary mode of action for topical retinoid therapy is the normalization of the abnormal follicular epithelial desquamation that leads to formation of the microcomedone. The microcomedone then progresses either down a noninflammatory pathway to comedone formation or toward inflammatory lesions.[1]

The first topical retinoid approved for the treatment of acne was a hydroalcoholic solution of tretinoin in a 0.05% concentration. This formulation was associated with substantial levels of irritation, with up to 20% of patients experiencing the development of new papules and pustules during the first few weeks of treatment (n=103).[2] The acne flaring seen with the original topical retinoid formulation has come to be viewed as a potential problem with topical retinoids in general.

Since the appearance of the first topical retinoid formulation, many different formulations of tretinoin have been developed. Newer retinoids such as adapalene and tazarotene, which are molecules that bind to retinoid receptors, have been developed.[3,4] These new formulations have been shown to reduce

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the number of inflammatory lesions with time.[5] This effect is attributed to a decrease in the precursor lesion (the microcomedone) and a decrease in the expression of toll-like receptors, which are the ligands for *Propionibacterium acnes* activation of inflammation.[6] Despite these findings, many dermatologists have concerns about using topical retinoids in the early stages of treating a patient with inflammatory acne. There is concern that topical retinoids may promote an increase in inflammatory lesions during the first weeks of treatment, as was clearly seen with the first formulation of hydroalcoholic tretinoin 0.05%.[2]

In 2006, a crystalline suspension of clindamycin phosphate 1.2%–tretinoin 0.025% in a gel formulation (CLIN/RA) was approved by the US Food and Drug Administration for the topical treatment of acne vulgaris in patients 12 years and older. The clinical trials for this combination therapy included an evaluation point after 2 weeks of treatment, which provided the opportunity to determine if a flare in inflammatory lesions occurred in participants who were treated with tretinoin gel 0.025% (RA) monotherapy compared with participants treated with CLIN/RA. Results on the clinical safety and efficacy of CLIN/RA have been published elsewhere.[7]

Methods

In 3 multicenter, double-blind, randomized, phase 3 trials, lesion counts were obtained 2 weeks following initiation of treatment.[7] In 2 of the trials, participants were randomly assigned to 1 of 4 study groups: CLIN/RA, clindamycin phosphate gel 1.2% (CLIN), RA, or vehicle gel (VEH). The third trial randomized participants to either CLIN/RA or CLIN.[7]

Participant Selection—Eligibility criteria for the 3 studies were 20 to 100 noninflammatory lesions, 20 to 50 inflammatory lesions, and 2 or fewer nodules.[7] Mandatory washout periods were required for all topical and systemic treatments. Acne severity for each participant at baseline according to the evaluator's global severity score (EGSS) was mild, moderate, or severe (EGSS scores of 2, 3 or 4, respectively). All participants were instructed to apply the gel once daily at bedtime after cleansing the face.[7]

Primary End Points—After 2 weeks of treatment, inflammatory lesions were counted for each participant and EGSS scores were evaluated without reference to baseline evaluations. The following measures of flaring were assessed: an increase in inflammatory lesions of 10% or greater or 20% or greater versus baseline.[7]

Statistical Analysis—The data from the 3 clinical studies were analyzed post hoc for the number and proportion of participants in each treatment group who showed a 10% or greater (or 20% or greater) increase in inflammatory lesions from baseline to week 2, and also were stratified according to baseline EGSS score (mild, moderate, severe). Within each stratum, the proportions were analyzed using the Pearson χ^2 test. The *P* values for statistical comparison of treatments within each stratum were cited as either the overall χ^2 *P* value with all 4 treatments included if $P>.05$ or the χ^2 of the pairwise analysis including only 2 treatments at a time for overall $P\leq.05$.

Results

Participants—A total of 4550 participants were randomly assigned to treatment groups in the 3 trials.[7] Study 1 enrolled 1252 participants, with 420 in the CLIN/RA group, 208 in the CLIN group, 417 in the RA group, and 207 in the VEH group. A total of 1288 participants were enrolled in study 2, with 425 participants in the CLIN/RA group, 218 in the CLIN group, 429 in the RA group, and 216 in the VEH group. The third trial recruited 2010 participants, with 1008 randomized to CLIN/RA and 1002 to CLIN.[7]

There were no significant differences between participants in the 3 studies for age, gender, or race.[7] Participants ranged in age from 11 to 59 years (mean, 18.98 years). There were no significant differences in the distribution of EGSS scores, with 74% of participants (3355/4550) considered to have moderate acne at baseline. The numbers of inflammatory, noninflammatory, and total acne lesions were comparable in all treatment groups at baseline. There was a mean of 29 inflammatory (range, 4–63), 49 noninflammatory (range, 9–141), and 78 total acne lesions (range, 21–195) per participant in each treatment group.[7]

Incidence of Flares—The proportion of participants in each treatment group who showed a 10% or greater (or 20% or greater) increase in inflammatory lesions following 2 weeks of treatment are shown in Figures 1 and 2.[7,8] The analysis was further stratified by severity of acne at baseline (mild, moderate, severe). In participants with mild acne at baseline (EGSS score, 2) treated with CLIN or RA monotherapy, there was a trend of a higher percentage of increased inflammatory lesions compared with participants treated with VEH (≥10%, $P=.312$; ≥20%, $P=.449$). However, there was no trend of a higher percentage of flare in participants treated with CLIN/RA compared with CLIN monotherapy. In participants with moderate and severe acne at baseline (EGSS scores of 3 or 4, respectively), the percentage of participants with either a 10% or greater (or 20% or greater) increase in inflammatory lesions was consistently higher in

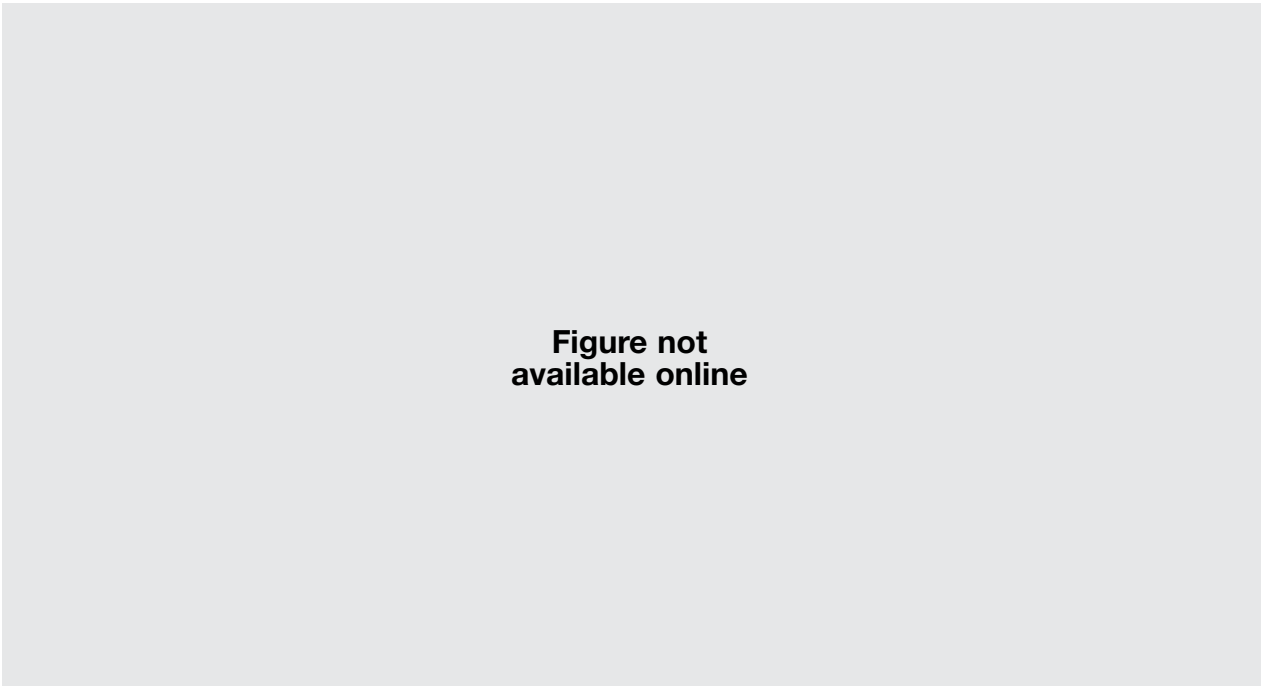

Figure 1. Participants with acne flare (≥10% increase in inflammatory lesions) at 2-week follow-up. Reprinted with permission from Del Rosso.[8] Copyright 2008 Matrix Medical Communications. All rights reserved.

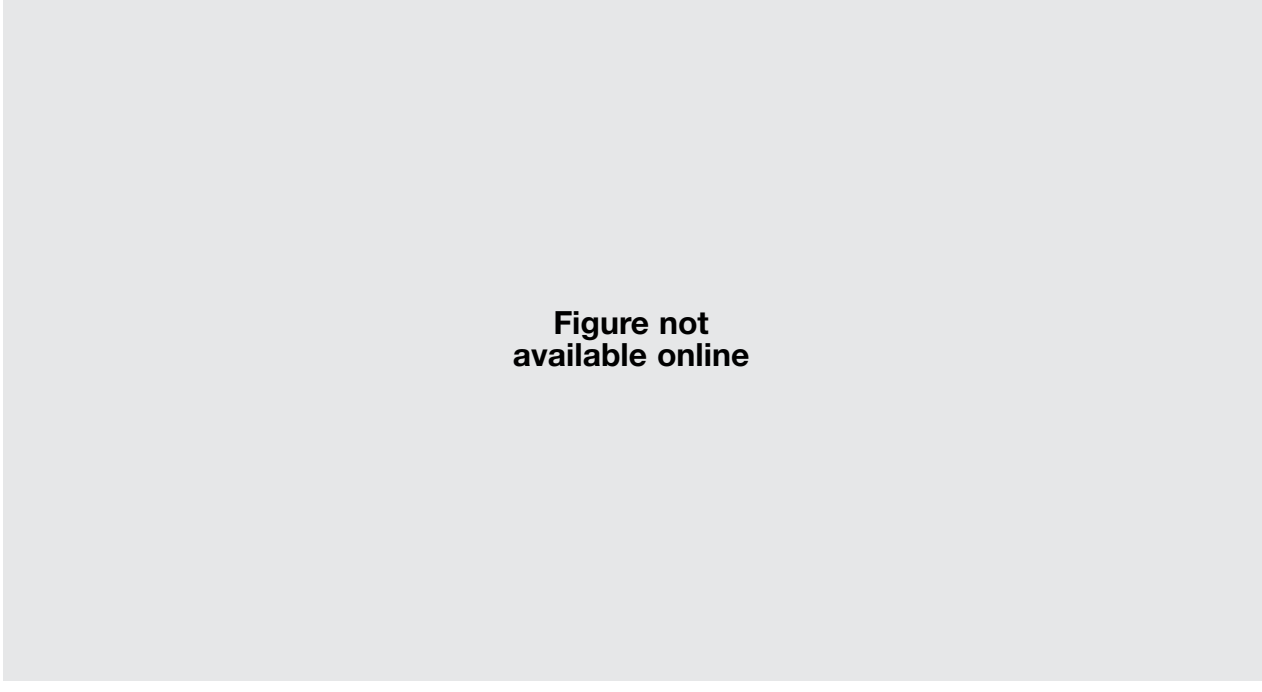

Figure 2. Participants with acne flare (≥20% increase in inflammatory lesions) at 2-week follow-up. Reprinted with permission from the *Journal of Drugs in Dermatology.* Copyright 2007.[7]

VEH-treated participants. Participants treated with CLIN/RA had comparable numbers of flares as participants treated with CLIN monotherapy. Participants treated with RA monotherapy had higher percentages of increased lesions than those treated with CLIN/RA or CLIN monotherapy.

Most participants experienced an improvement in acne lesions. Improvements (≥10% decrease in number of lesions at the 2-week follow-up compared with baseline) were noted for more than 60% of participants in the CLIN/RA, CLIN, RA, and VEH treatment groups (Table 1). A similar pattern was

Table 1.

Participants With ≥10% Improvement, No Change, or ≥10% Flare After 2 Weeks of Study Treatment Stratified by Baseline Acne Severity

	CLIN/RA, n (%) (n=1853)	CLIN, n (%) (n=1428)	RA, n (%) (n=846)	VEH, n (%) (n=423)
Mild Acne at Baseline (EGSS score, 2)				
n	118	52	91	46
Improvement: ≥10% decrease in lesions	85 (72.0)	40 (76.9)	60 (65.9)	34 (73.9)
No change: ±10% change in lesions	24 (20.3)	7 (13.5)	17 (18.7)	8 (17.4)
Flare: ≥10% increase in lesions	9 (7.6)	5 (9.6)	14 (15.4)	4 (8.7)
Moderate Acne at Baseline (EGSS score, 3)				
n	1358	1048	635	314
Improvement: ≥10% decrease in lesions	982 (72.3)	724 (69.1)	414 (65.2)	192 (61.1)
No change: ±10% change in lesions	260 (19.1)	223 (21.3)	123 (19.4)	67 (21.3)
Flare: ≥10% increase in lesions	116 (8.5)	101 (9.6)	98 (15.4)	55 (17.5)
Severe Acne at Baseline (EGSS, ≥4)				
n	375	327	118	63
Improvement: ≥10% decrease in lesions	249 (66.4)	210 (64.2)	74 (62.7)	35 (55.6)
No change: ±10% change in lesions	81 (21.6)	81 (24.8)	29 (24.6)	13 (20.6)
Flare: ≥10% increase in lesions	45 (12.0)	36 (11.0)	15 (12.7)	15 (23.8)

Abbreviations: CLIN/RA, clindamycin phosphate 1.2%–tretinoin 0.025% gel; CLIN, clindamycin phosphate gel 1.2%; RA, tretinoin gel 0.025%; VEH, vehicle gel; EGSS, evaluator's global severity score.

evident when the 20% or greater measure was used to determine flare rates at the 2-week follow-up (Table 2).

Among participants who experienced an increase in inflammatory lesions of 10% or greater following 2 weeks of treatment (Figure 1), participants with moderate acne who received CLIN/RA had significantly lower rates of flaring than participants treated with RA or VEH, as did participants receiving CLIN monotherapy ($P<.001$ for all comparisons). Flaring rates between the CLIN/RA and CLIN treatment groups were not significantly different ($P=.352$). Rates of flaring were not significantly different among participants with moderate acne who received RA monotherapy compared with participants who received VEH ($P=.412$). For participants with severe acne, the overall treatment effect was statistically significant ($P=.044$), and post hoc analysis revealed that CLIN/RA and CLIN monotherapy significantly reduced flaring relative to VEH ($P=.012$ and $P=.006$, respectively), while RA monotherapy tended to reduce flaring rates more than

Table 2.

Participants With ≥20% Improvement, No Change, or ≥20% Flare After 2 Weeks of Study Treatment Stratified by Baseline Acne Severity

	CLIN/RA, n (%) (n=1853)	CLIN, n (%) (n=1428)	RA, n (%) (n=846)	VEH, n (%) (n=423)
Mild Acne at Baseline (EGSS score, 2)				
n	118	52	91	46
Improvement: ≥20% decrease in lesions	72 (61.0)	34 (65.4)	50 (54.9)	25 (54.3)
No change: ±20% change in lesions	41 (34.7)	14 (26.9)	32 (35.2)	18 (39.1)
Flare: ≥20% increase in lesions	5 (4.2)	4 (7.7)	9 (9.9)	3 (6.5)
Moderate Acne at Baseline (EGSS score, 3)				
n	1358	1048	635	314
Improvement: ≥20% decrease in lesions	861 (63.4)	626 (59.7)	348 (54.8)	161 (51.3)
No change: ±20% change in lesions	421 (31.0)	346 (33.0)	222 (35.0)	115 (36.6)
Flare: ≥20% increase in lesions	76 (5.6)	76 (7.3)	65 (10.2)	38 (12.1)
Severe Acne at Baseline (EGSS, ≥4)				
n	375	327	118	63
Improvement: ≥20% decrease in lesions	200 (53.3)	173 (52.9)	58 (49.2)	23 (36.5)
No change: ±20% change in lesions	147 (39.2)	132 (40.4)	50 (42.4)	32 (50.8)
Flare: ≥20% increase in lesions	28 (7.5)	22 (6.7)	10 (8.5)	8 (12.7)

Abbreviations: CLIN/RA, clindamycin phosphate 1.2%–tretinoin 0.025% gel; CLIN, clindamycin phosphate gel 1.2%; RA, tretinoin gel 0.025%; VEH, vehicle gel; EGSS, evaluator's global severity score.

VEH (P=.056). Otherwise, rates of flaring did not differ significantly between the treatment groups.

Among participants who experienced an increase in inflammatory lesions of 20% or greater following 2 weeks of treatment (Figure 2), participants with moderate acne who received CLIN/RA or CLIN monotherapy had significantly less flaring than the RA monotherapy group (P<.001 and P=.032, respectively) or the VEH group (P<.001 and P=.032, respectively). Flaring rates in the CLIN/RA and CLIN monotherapy groups did not differ significantly from one another (P=.098), and flaring rates in the RA group did not differ significantly from the VEH group (P=.385). For participants with severe acne, the treatment groups did not differ significantly from one another (P=.427).

Comment

Acne flaring (ie, an increase in inflammatory lesions) during topical retinoid therapy was described with the first RA formulation. This hydroalcoholic solution was estimated to produce an acute flaring of papules

and pustules in up to 20% of patients.[2] Subsequent to this report, several formulations of RA, and more recently adapalene and tazarotene, have been developed and studied in clinical trials. Although all of these trials have shown a decrease in inflammatory lesions with time, evaluation at early time points was not done and thus potential aggravation and worsening of acne in a subset of participants could have been missed. In these 3 large clinical trials, evaluation after 2 weeks of treatment provided an opportunity to assess if this formulation of RA, alone or in combination with CLIN, was associated with aggravation of the inflammatory phase of acne.

If the RA in this formulation was aggravating inflammatory acne, one would anticipate seeing a higher percentage of participants showing an increase in inflammatory lesions than participants treated with VEH and/or an increase in inflammatory lesions in participants treated with CLIN/RA compared with CLIN monotherapy. We chose 2 measures to assess flaring: an increase in inflammatory lesions of 10% or greater or 20% or greater. There was some evidence of RA aggravation of inflammatory acne in that nearly twice as many participants with mild acne at baseline showed an increase in inflammatory lesions of 10% or greater or 20% or greater compared with participants treated with VEH monotherapy. However, no increase was found in participants treated with CLIN/RA compared with participants treated with CLIN monotherapy. Participants with moderate acne treated with RA had a greater incidence of an increase in inflammatory lesions of 10% or greater compared with the CLIN and CLIN/RA cohorts but less than participants treated with VEH. These differences may reflect greater anti-inflammatory benefit for CLIN/RA and CLIN monotherapy after 2 weeks of treatment. Because the incidence of participants with increased numbers of inflammatory lesions was less than in the VEH-treated group, there is no signal for retinoid aggravation of inflammation. Interestingly, the greatest difference between RA and VEH was found in individuals with severe inflammatory acne, with no suggestion of RA aggravation.

The lack of aggravation of the inflammatory phase of acne with this CLIN/RA combination formulation may result from 1 or more factors, including the anti-inflammatory effects of CLIN and the formulation that consists of partial solubilization combined with a crystalline suspension of RA. The reduced inflammation does not appear to be related to a reduction in efficacy of the combination product because in 2 phase 3 trials, CLIN/RA gel produced significant clinical improvements compared with CLIN or RA monotherapy or VEH ($P<.001$).[7] The failure to observe an increased rate of inflammatory lesions in participants with moderate to severe acne at baseline who were treated with topical RA monotherapy indicates the need for additional research to determine if acne flares occur in individuals treated with other formulations of RA or other topical retinoids.

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