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Efficacy and safety of clindamycin phosphate 1.2%/tretinoin 0.025% formulation for the treatment of acne vulgaris: pooled analysis of data from three randomised, double-blind, parallel-group, phase III studies

Background: The efficacy and safety of clindamycin phosphate 1.2%/tretinoin 0.025% (Clin-RA) were evaluated in three 12-week randomised studies. **Objectives:** To perform a pooled analysis of data from these studies to evaluate Clin-RA's efficacy and safety in a larger overall population, in subgroups of adolescents and according to acne severity. **Materials & Methods:** 4550 patients were randomised to Clin-RA, clindamycin, tretinoin and vehicle. Evaluations included percentage change in lesions, treatment success rate, proportions of patients with $\geq 50\%$ or $\geq 80\%$ continuous reduction in lesions, adverse events and cutaneous tolerability. **Results:** In the overall population, the percentage reduction in inflammatory, non-inflammatory and total lesions and the treatment success rate were significantly greater with Clin-RA compared with clindamycin, tretinoin and vehicle alone (all $p < 0.01$). The percentage reduction in all types of lesions was also significantly greater with Clin-RA in the adolescent subgroup (2915 patients, $p < 0.002$) and in patients with mild/moderate acne (3662 patients, $p < 0.02$) versus comparators. In patients with severe acne ($n = 880$), the percentage reduction in all lesion types was significantly greater with Clin-RA versus vehicle ($p < 0.0001$). A greater proportion of Clin-RA treated patients had a $\geq 50\%$ or $\geq 80\%$ continuous reduction in all types of lesions at week 12 compared with clindamycin, tretinoin and vehicle. Adverse event frequencies in the active and vehicle groups were similar. Baseline-adjusted mean tolerability scores over time were < 1 (mild) and similar in all groups. **Conclusion:** Clin-RA is safe, has superior efficacy to its component monotherapies and should be considered as one of the first-line therapies for mild-to-moderate facial acne.

Key words: acne vulgaris, clindamycin phosphate, combination therapy, pooled analysis, tretinoin

Both consensus papers from the Global Alliance to Improve Outcomes in Acne and the current S3 guidelines from the European Dermatology Forum recommend combination treatment with topical retinoids and antimicrobials as the cornerstone of acne management [1-3]. The pathogenesis of acne involves four main factors: excess sebum production, bacterial hypercolonisation, disturbed keratinisation within the follicle and inflammation by hyperactive innate and adapted immunity [1]. Combination therapy with a topical retinoid and antimicrobial has the advantage that the two treatments have complementary mechanisms of action which results in an increased spectrum of activity against the pathogenic factors for acne compared with either monotherapy alone [1]. Retinoids target microcomedones, are comedolytic and anticomedogenic, normalise desquamation and have some anti-inflammatory properties, whereas antibiotics target *P. acnes* and also have anti-inflammatory actions [1]. In addition, clindamycin may have some anticomedogenic effect

[4]. Consequently, combinations of these products can effectively target both inflammatory and non-inflammatory acne lesions [5]. In contrast, combination products which contain two different antimicrobial agents, such as an antibiotic and benzoyl peroxide (BPO), have a more restricted range of actions as they do not contain a retinoid which is both comedolytic and anticomedogenic. An additional benefit of retinoid/antibiotic combinations is that they result in more rapid and better efficacy than antibiotic monotherapy, possibly due to the retinoid normalising desquamation and facilitating penetration of the antibiotic into the subcutaneous follicle [1, 6-8]. This action may potentially decrease the exposure to antibiotics, so reducing the likelihood of antibiotic resistance occurring.

Clindamycin phosphate 1.2%/tretinoin 0.025% (Clin-RA) is a fixed-dose antibiotic/retinoid combination product which has been shown to be more effective for the treatment of acne than its individual active components [9]. Clin-RA (marketed under several names in Europe including

Acnatac[®] and Treclinac[®], and as Ziana[®] in the US) contains clindamycin together with solubilised and crystalline tretinoin in a patented, alcohol-free, aqueous-based gel [10]. The solubilised form of tretinoin is immediately available, whilst the crystalline form allows slow dissolution and sustained cutaneous penetration [10]. The particle size of tretinoin is optimised to enhance follicular penetration [10]. The characteristics of this formulation, together with the anti-inflammatory properties of clindamycin [11, 12], may account for the favourable cutaneous tolerability profile and low irritation potential of Clin-RA compared with other retinoid-based formulations [10, 11, 13]. Indeed, a recent comparative study demonstrated that Clin-RA produced significantly less stinging/burning and itching than a combination containing adapalene 0.1% and BPO 2.5% [14]. Another product has been developed which also contains clindamycin phosphate 1.2%/tretinoin 0.025% in a different vehicle and with a different type of tretinoin (i.e., Velac[®]/Velтин[™]), but this is not the subject of the current analysis.

The objective of the current investigation was to pool the results of three, 12-week, multicentre, randomised, double-blind, parallel group, phase III studies of Clin-RA, clindamycin, tretinoin and vehicle gels to evaluate the efficacy and safety of Clin-RA in a larger overall patient population. Subgroup analyses were also carried out to investigate the efficacy of Clin-RA in adolescent patients (aged 11–17 years) and according to the severity of acne. This analysis also investigated the proportion of patients in each treatment group who achieved a $\geq 50\%$ or $\geq 80\%$ continuous reduction in acne lesions. These novel efficacy endpoints assess how quickly and in how many patients a pre-defined response is achieved and sustained for the study duration.

Methods

Overview of studies

This pooled analysis included data from three, multicentre, randomised, double-blind, parallel group, phase III studies of Clin-RA which have been reported in full previously [9]. Clinical studies of another product which also contains clindamycin phosphate 1.2% and tretinoin 0.025% in a different vehicle (i.e., Velac[®]/Velтин[™]) were not included in the current analysis. In two of the included studies, patients were randomised to Clin-RA, clindamycin phosphate 1.2%, tretinoin 0.025%, or vehicle gels (Study reference numbers: G2HP-06-02 and G2HP-07-02) [9]. In the third included study, patients were randomised to gels containing either Clin-RA or clindamycin phosphate 1.2% (Study reference number: MP-1501-02) [9]. In each study, topical applications of the study materials were made to the entire face (excluding the mouth, eyes, and lips) once daily before bedtime for 12 weeks. All three studies were conducted in accordance with Good Clinical Practice, the Declaration of Helsinki and all relevant local regulations. All patients provided written and verbal informed consent before participating in a study. Our analysis differs from that of Schlessinger *et al* which only pooled efficacy data from studies G2HP-06-02 and G2HP-07-02 and reported study MP-1501-02 separately [9].

Patients

To be included in a study, patients had to be at least 12 years old with 20–50 facial inflammatory (papules and pustules), 20–100 non-inflammatory (open and closed comedones) acne lesions, and no more than two nodules (defined as inflammatory lesions ≥ 5 mm in diameter). Patients had a baseline Evaluator's Global Severity Score (EGSS) [9] of 2 (mild acne) to 4 (severe) in studies G2HP-06-02 and G2HP-07-02, and 3 or 4 in study MP-1501-02. Patients with facial beards or moustaches or with facial dermatological conditions such as acne conglobata or acne fulminans that could interfere with clinical evaluations were excluded from the studies as were patients with any underlying disease or facial dermatological condition that required treatment with interfering topical or systemic therapy (hormonal contraception was permitted). Other exclusion criteria included a history of regional enteritis, ulcerative colitis or antibiotic associated colitis; and concomitant use of over-the-counter products containing BPO, retinol, or alpha-hydroxy-, salicylic- or glycolic acids.

Efficacy and safety assessments

In this pooled analysis, the efficacy variables included the percentage change in inflammatory, non-inflammatory and total lesions from baseline to week 12, and the treatment success rate defined as the percentage of patients who were clear or almost clear on the EGSS scale of acne severity or who had at least a 2 grade improvement in their EGSS score at week 12 (scores range from 0 to 5) [9]. Lesion counts and EGSS assessments were performed at baseline and at weeks 2, 4, 8 and 12. The percentage change in lesions was also assessed in the following subgroups: adolescent patients (aged 11–17 years, $n = 2915$), patients with mild/moderate acne (EGSS of 2 or 3; $n = 3662$), and patients with severe acne (EGSS of 4, $n = 880$). Treatment success was evaluated in the adolescent subgroup. Although the studies were designed to enrol children aged 12 years or over, six patients aged 11 years were also entered and are included in the analyses.

Efficacy was also assessed by determining the proportion of patients in the overall population in each treatment group who had a $\geq 50\%$ or $\geq 80\%$ continuous reduction in inflammatory, non-inflammatory, or total lesions, and the time to achieve these responses. Patients were classified as having a continuous response at each efficacy assessment time point (i.e., weeks 2, 4, 8, or 12) if they had a $\geq 50\%$ or $\geq 80\%$ reduction in lesions that was then sustained for the rest of the study.

Adverse events were recorded at weeks 2, 4, 8 and 12. Tolerability scores for erythema, burning, scaling, stinging and itching were also evaluated at these time points and at baseline, and were rated as none (0), mild (1), moderate (2), and severe (3).

Statistical analyses

The efficacy analyses were conducted on the overall intention-to-treat population defined as all patients who were randomised and received a study drug. Median percentage changes from baseline to week 12 in lesion counts were calculated, given that the distribution of

data was skewed. Statistical significance was assessed using a ranked ANOVA model with the factors treatment, study and study centre nested under study, and interaction between treatment group and study centre. The Cochran-Mantel-Haenszel test stratified by study and study centre was used to evaluate the treatment success rate at week 12. Median percentage changes in lesion counts from baseline to week 12 were also analysed in the adolescent subgroup (aged 11–17 years) and the subgroups of patients with mild/moderate and severe acne. Responder rates were estimated using Kaplan-Meier product-limit estimates with pairwise log-rank tests being used to assess treatment differences regarding the time to response. All significance tests between Clin-RA and clindamycin were performed using the data from three studies, whereas comparisons of Clin-RA *versus* tretinoin and vehicle were based on data from studies G2HP-06-02 and G2HP-07-02 since tretinoin and vehicle were not included in study MP-1501-02. All significance tests were two-sided at the 0.05 level. Changes from baseline in tolerability scores were summarised descriptively.

Results

Patient baseline demographics and clinical characteristics

In total, 4550 patients from the three pivotal studies were included in this analysis. Of these, 1853 patients were treated with Clin-RA, 1428 with clindamycin, 846 with tretinoin and 423 with vehicle. The overall proportion of patients who completed the studies was high (84.4%) and similar for each treatment group (figure 1). For patients who

discontinued treatment, the profile of reasons for discontinuation was similar across treatment groups (figure 1). The treatment groups were well matched at baseline in terms of demographics and dermatological characteristics (table 1). Most of the patients had mild/moderate (80.5%) rather than severe acne (19.3%), according to the EGSS.

Efficacy endpoints: overall population

Clin-RA was significantly more effective than clindamycin, tretinoin and vehicle in terms of the median percentage change from baseline to week 12 in inflammatory (65.2% *vs* 60.0%, 46.4% and 32.3%, respectively), non-inflammatory (51.6% *vs* 43.5%, 37.3% and 23.9%) and total lesions (54.5% *vs* 48.1%, 39.6% and 22.8%) in the overall population (all $p < 0.01$ *vs* Clin-RA; figure 2). The monotherapy components of Clin-RA had complementary effects.

The frequency of treatment success assessed at week 12 in the overall population was significantly greater with Clin-RA compared with clindamycin, tretinoin and vehicle (32.1% *vs* 27.9%, 17.4% and 9.9%, respectively, all $p \leq 0.0001$).

Efficacy endpoints: subgroup analyses

In the adolescent subgroup (patients aged 11–17 years), Clin-RA was significantly more effective than clindamycin, tretinoin and vehicle in terms of the median percentage change from baseline to week 12 in inflammatory (62.5% *vs* 58.3%, 40.7% and 21.4%, respectively), non-inflammatory (50.0% *vs* 42.2%, 32.8% and 13.5%) and total lesions (52.5% *vs* 46.4%, 35.6% and 14.6%) (all $p < 0.002$ *vs* Clin-RA; figure 2). The treatment difference between Clin-RA and vehicle for the median percentage change from baseline to week 12 in inflammatory, non-inflammatory and

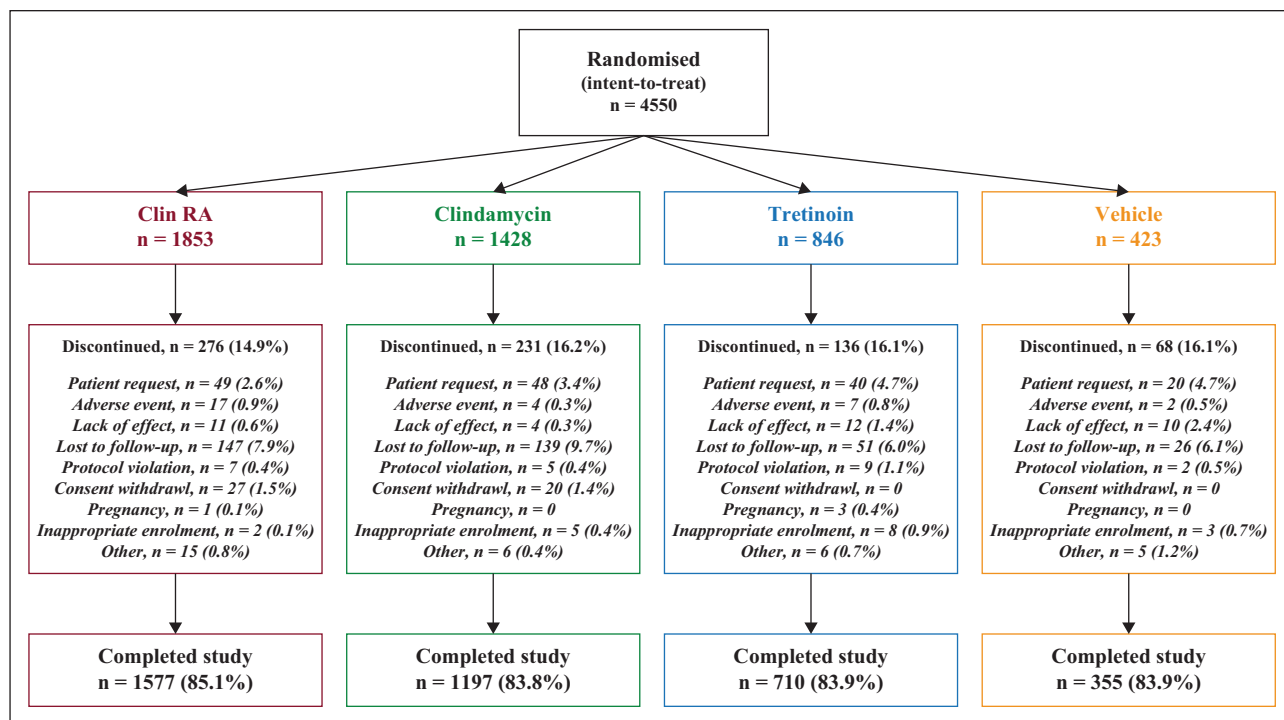


Figure 1. Patient disposition.

Table 1. Patient baseline demographics and clinical characteristics

Characteristic	Clin-RA N = 1853	Clindamycin N = 1428	Tretinoin N = 846	Vehicle N = 423	Overall N = 4550
Age, years Mean (SD)	19.2 (7.4)	19.8 (7.2)	19.7 (7.7)	19.4 (7.7)	19.3 (7.4)
Age: 11–17 years n (%)	1,189 (64.2)	919 (64.4)	532 (62.9)	275 (65.0)	2915 (64.1)
Female n (%)	926 (50.0)	749 (52.5)	438 (51.8)	220 (52.0)	2333 (51.3)
White n (%)	1381 (74.5)	1058 (74.1)	577 (68.2)	286 (67.6)	3302 (72.6)
Acne severity					
Mild/moderate, n (%)	1476 (79.7)	1100 (77.0)	726 (85.8)	360 (85.1)	3662 (80.5)
Severe, n (%)	374 (20.2)	326 (22.8)	118 (13.9)	62 (14.7)	880 (19.3)
Median lesion count (range)					
Overall population					
Inflammatory	28 (4-54)	28 (17-63)	27 (5-54)	27 (20-54)	28 (4-63)
Non-inflammatory	44 (14-141)	44 (15-100)	44 (11-126)	44 (9-110)	44 (9-141)
Total	74 (24-195)	75 (38-150)	73 (21-156)	72 (29-145)	74 (21-195)
Age: 11–17 years					
Inflammatory	29 (20-54)	29 (17-63)	28 (13-54)	29 (20-54)	29 (13-63)
Non-inflammatory	47 (19-141)	49 (15-100)	50 (19-126)	47 (20-110)	48 (15-141)
Total	79 (39-195)	79 (38-150)	82 (41-156)	80 (41-145)	79 (38-195)

SD, standard deviation.

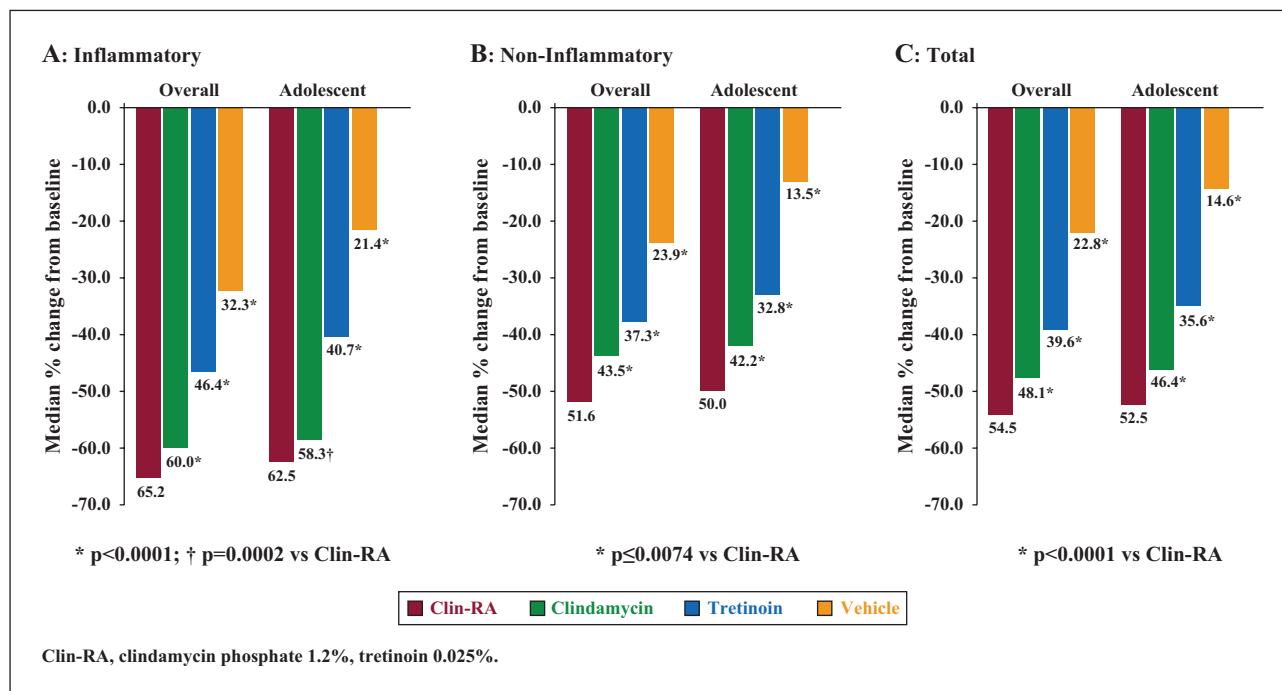


Figure 2. Median percentage change in inflammatory (A), non-inflammatory (B) and total lesion counts (C) in the overall and adolescent populations after 12 weeks of treatment.

total lesions was higher in the adolescent compared with the overall population. The frequency of treatment success assessed at week 12 in the adolescent subgroup was significantly greater with Clin-RA compared with clindamycin,

tretinoin and vehicle (30.5% vs 27.6%, 13.5% and 6.2%, respectively, all $p \leq 0.0023$). Clin-RA was significantly more effective than clindamycin, tretinoin and vehicle in terms of the median percentage

change from baseline to week 12 in inflammatory (65.5% vs 60.7%, 46.4% and 33.3%, respectively), non-inflammatory (51.4% vs 43.4%, 37.3% and 24.8%) and total lesions (54.5% vs 47.6%, 39.7% and 25.0%) in the subgroup of patients with mild/moderate acne (all $p < 0.02$ vs Clin-RA; *figure 3*). The median percentage changes from baseline to week 12 in inflammatory (63.7% vs 19.6%), non-inflammatory (53.4% vs 19.0%) and total lesions (54.4% vs 11.8%) were also significantly greater with Clin-RA compared with vehicle in patients with severe acne (all $p < 0.0001$ vs Clin-RA). The magnitude of the median percentage change from baseline to week 12 in inflammatory, non-inflammatory and total lesions with Clin-RA was comparable in patients with mild/moderate and severe acne (*figure 3*). However, the treatment difference between Clin-RA and vehicle for the median percentage change from baseline to week 12 in inflammatory, non-inflammatory and total lesions was higher in patients with severe acne compared to those with mild/moderate disease.

Responder rates

The proportion of Clin-RA treated patients who had a $\geq 50\%$ continuous reduction in inflammatory lesions at week 12 estimated using Kaplan-Meier curves was greater than with clindamycin, tretinoin or vehicle (64% vs 59%, 46% and 34%, respectively; *figure 4A*). Similarly, a greater proportion of Clin-RA treated patients had a $\geq 50\%$ continuous reduction in non-inflammatory (51% vs 43%, 36% and 22%) and total lesions (55% vs 47%, 38% and 24%) at week 12 compared with clindamycin, tretinoin and vehicle (*figures 4B and C*). A $\geq 50\%$ continuous reduction

in total lesions was achieved up to 4 weeks faster with Clin-RA compared with clindamycin, tretinoin and vehicle ($p < 0.001$).

For all treatment groups, the proportion of patients achieving a continuous response was lower at the more stringent $\geq 80\%$ threshold. A greater proportion of patients treated with Clin-RA compared with clindamycin, tretinoin and vehicle had a $\geq 80\%$ continuous reduction in inflammatory (31% vs 26%, 14% and 12%, respectively), non-inflammatory (16% vs 11%, 7% and 6%), and total lesions (17% vs 13%, 7% and 5%) at week 12 (*figures 4D-F*). A $\geq 80\%$ continuous reduction in total lesions was achieved up to 4 weeks faster with Clin-RA compared with clindamycin, tretinoin and vehicle ($p \leq 0.0035$).

Safety and tolerability

The percentage of patients reporting at least one adverse event rated as possibly, probably or related to study treatment across the three studies was low in each group (Clin-RA 4%, clindamycin 2%, tretinoin 4%, vehicle 2%). Clin-RA was well tolerated with erythema, burning, scaling, stinging and itching being absent in the majority of patients. The baseline-adjusted mean tolerability scores over time for erythema, burning, scaling, stinging and itching were less than 1 (mild) and comparable in the different treatment groups. The tolerability scores with Clin-RA were lower than the sum of the scores for the monotherapies (*figure 5*). Overall, Clin-RA was not associated with any new safety concerns compared with its constituent monotherapies.

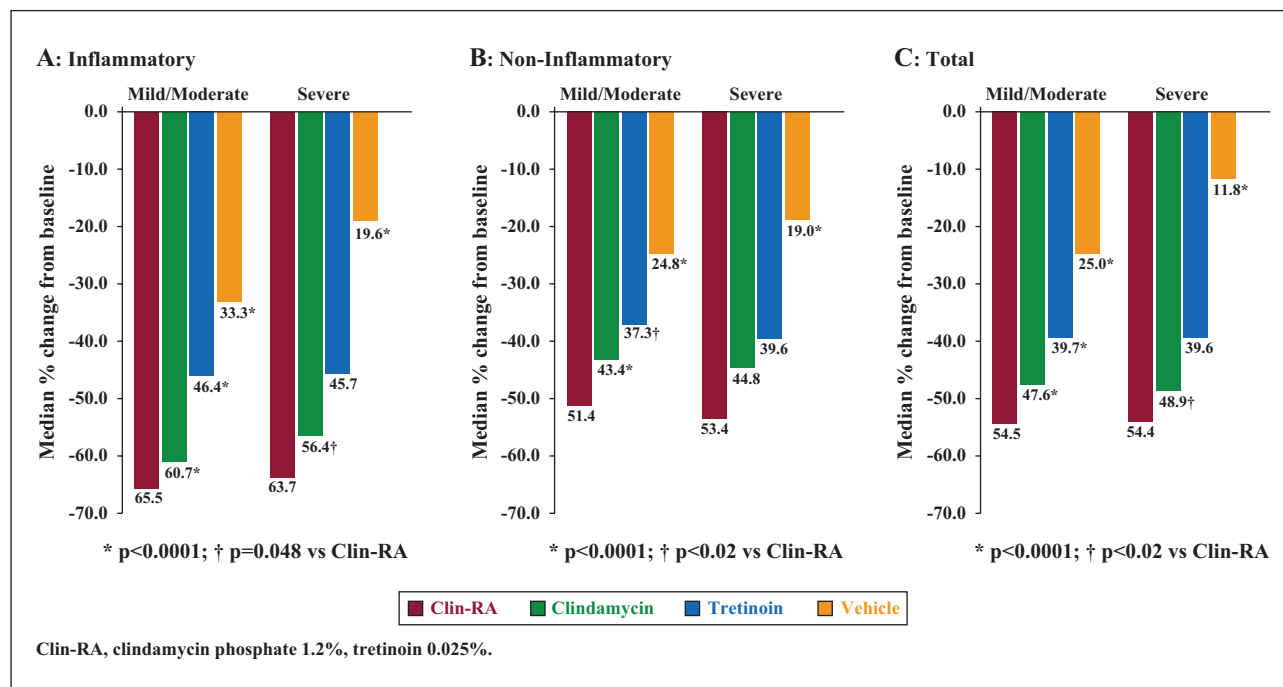


Figure 3. Median percentage change in inflammatory (A), non-inflammatory (B) and total lesion counts (C) in patients with mild/moderate and severe acne after 12 weeks of treatment.

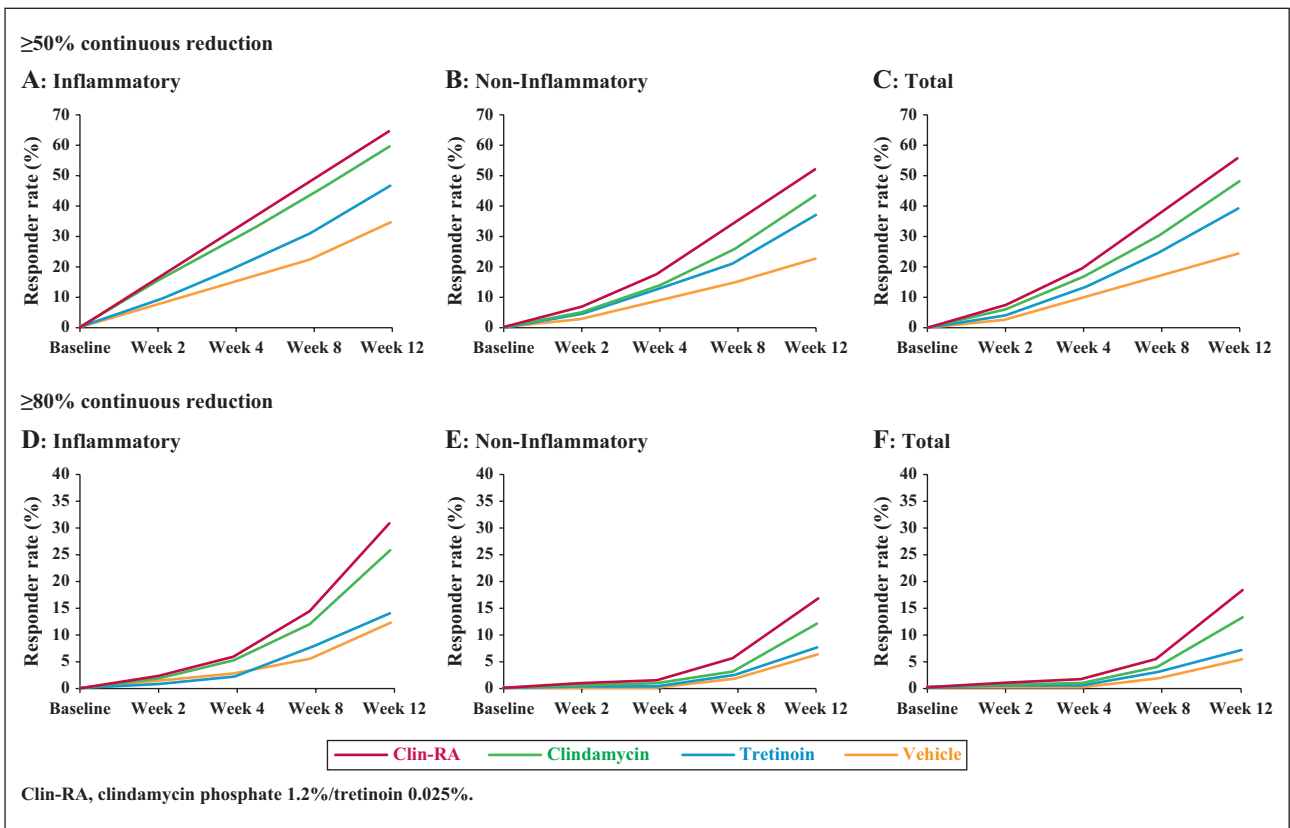


Figure 4. Proportion of patients with $\geq 50\%$ continuous reduction in inflammatory (A), non-inflammatory (B) and total lesion counts (C), and $\geq 80\%$ continuous reduction in inflammatory (D), non-inflammatory (E) and total lesion counts (F).

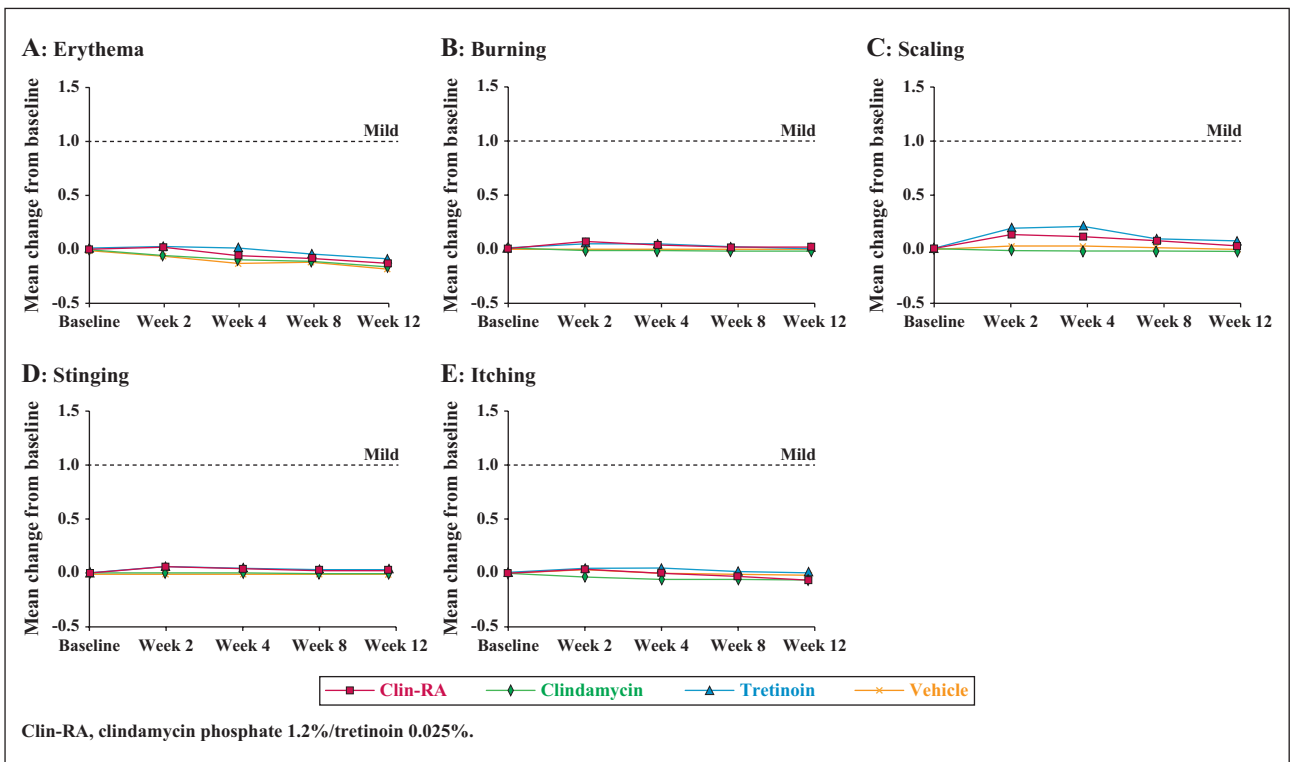


Figure 5. Baseline-adjusted mean tolerability scores for erythema (A), burning (B), scaling (C), stinging (D), itching (E).

Discussion

The results of this pooled analysis of data from three pivotal phase III studies demonstrate that Clin-RA provides significantly greater percentage reductions in both inflammatory and non-inflammatory acne lesions compared with clindamycin and tretinoin monotherapy, confirming the results of the individual clinical studies [9]. The treatment success rate was also significantly higher with Clin-RA *versus* its monotherapies with approximately one in three acne patients being clear or almost clear of their acne or having a significant improvement in their acne after 12 weeks of treatment. The responder analysis indicated that one in every two patients treated with Clin-RA had a 50% or greater continuous reduction in total acne lesions and that one in every five Clin-RA treated patients had an 80% or greater continuous reduction in total acne lesions by week 12. These responses were achieved up to 4 weeks faster with Clin-RA compared with its monotherapies.

A total of 2915 of the patients (64.1%) in the current pooled analysis were adolescents aged 11–17 years. Acne vulgaris affects up to 80% of adolescents and can severely impact their quality of life [2]. Clin-RA provided a significantly greater percentage reduction in all lesion types and a significantly greater treatment success rate in the adolescent subgroup compared with clindamycin and tretinoin monotherapy. This subgroup analysis also indicates that the efficacy of Clin-RA in terms of percentage reduction in inflammatory, non-inflammatory and total lesions and treatment success rate is similar in the adolescent and overall populations.

Clin-RA was associated with significantly greater percentage reductions in inflammatory, non-inflammatory and total lesions compared with clindamycin, tretinoin and vehicle in patients with mild/moderate acne, classified using the EGSS. Statistical significance was not always achieved for the percentage reduction in lesions with Clin-RA compared with its monotherapies in patients with severe acne, due to the smaller sample size of these subgroups. However, the percentage reduction in lesion counts with Clin-RA was numerically similar in the subgroups of patients with mild/moderate and severe acne.

As anticipated, the current pooled analysis demonstrated that clindamycin was effective at reducing inflammatory acne lesions, which is consistent with its antibacterial mode of action [7]. This analysis also showed that clindamycin was effective against non-inflammatory lesions. This effect may be explained by the anti-inflammatory actions of clindamycin (e.g., inhibition of pro-inflammatory factors, chemokines and cytokines), especially given that inflammation may play a role in the very early stages of acne development [11, 12, 15]. In addition, evidence indicates that clindamycin may have an anticomedogenic effect [4]. However, clindamycin monotherapy is not currently recommended for the treatment of acne due to the growing problem of antibiotic resistance [1, 3].

Acne patients want treatments with a rapid and sustained onset of action and which are well tolerated. In particular, treatments which are associated with fast and substantial or complete clearance of acne lesions are highly desirable. In this study, continuous responder rates were assessed to determine the proportion of patients who achieved

a $\geq 50\%$ or $\geq 80\%$ reduction in lesions that was sustained for the duration of the study. The 50% response threshold may be considered to represent a substantial improvement in acne lesions, whereas the 80% response threshold may represent an almost complete reduction of acne lesions. A $\geq 50\%$ continuous reduction in total lesions was achieved in over 50% of Clin-RA treated patients, whereas a $\geq 80\%$ continuous reduction in total lesions was achieved in approximately 20% of Clin-RA treated patients. These responses were achieved up to 4 weeks faster with Clin-RA compared with clindamycin, tretinoin and vehicle monotherapy. The percentage of patients achieving a $\geq 50\%$ or $\geq 80\%$ continuous reduction in inflammatory lesions with clindamycin was only slightly lower than that achieved with Clin-RA. In contrast, the differences in response rates against non-inflammatory lesions between Clin-RA and clindamycin were more apparent. This suggests that the comedolytic and anticomedogenic actions of tretinoin and the anti-inflammatory and anticomedogenic effects of clindamycin together contribute to the effect of Clin-RA against non-inflammatory lesions, whereas the antibacterial and anti-inflammatory actions of clindamycin are the primary contributors to the effect of Clin-RA against inflammatory lesions. The current responder analysis also indicated that the proportion of patients who were treated with tretinoin and who achieved a $\geq 80\%$ continuous reduction in inflammatory, non-inflammatory and total lesions was only slightly greater than the respective proportion of vehicle-treated patients. In addition, the results showed that a high proportion (approximately 20–30%) of vehicle-treated patients achieved a $\geq 50\%$ continuous reduction in inflammatory, non-inflammatory and total lesions. However, the time to achieve a $\geq 50\%$ response was significantly shorter with both monotherapies and Clin-RA compared with vehicle. Overall, continuous lesion reductions represent a novel way of assessing the efficacy of acne treatments.

Clin-RA was shown to be safe and well tolerated in the current pooled analysis with no difference in safety outcomes compared with its individual components. This confirms the safety and tolerability profile reported in the individual clinical studies of Clin-RA and a similar profile was also observed in a long-term study of Clin-RA [9, 16]. The low levels of cutaneous irritation observed with Clin-RA and the tretinoin formulation used in the Clin-RA studies may be due to the water-based gel being less irritating than an alcohol-based gel. Furthermore, the combination of solubilised and crystalline tretinoin may minimise skin irritation, with the crystalline form being delivered into the skin in a slow and sustained manner [10]. This may be advantageous compared with other retinoid-based therapies which can be associated with cutaneous side effects in around 65 to 75% of patients [13]. A recent comparative study demonstrated that Clin-RA is better tolerated and associated with significantly less burning/stinging and itching than a fixed-dose combination of adapalene 0.1%/BPO 2.5% [14]. The anti-inflammatory properties of clindamycin may also contribute to the low irritation potential of Clin-RA. These effects include the inhibition of lipase production and release of leukocyte chemotactic factors by *P. acnes*, and the prevention of release of proinflammatory cytokines such as interleukin-1beta, interferon-gamma and tumour necrosis factor-alpha by cells such as monocytes, macrophages and keratinocytes [11, 12].

Fixed-dose combination products for acne, such as Clin-RA, offer patients several benefits compared with monotherapies. Firstly, the complementary mechanisms of action of clindamycin and tretinoin in Clin-RA enables three out of the four major pathogenic factors for acne to be targeted, namely disturbed desquamation, bacterial hypercolonisation and inflammation [1]. Secondly, retinoid/antibiotic combinations result in more rapid and better efficacy than antibiotic monotherapy, possibly due to the retinoid normalising desquamation and facilitating penetration of the antibiotic into the subcutaneous follicle [1, 6-8]. This action may potentially decrease the exposure to antibiotics so reducing the likelihood of antibiotic resistance occurring. Indeed, a 16-week study of Clin-RA versus clindamycin 1%/BPO 5% showed that neither fixed-dose combination product was associated with the development of clindamycin-resistant *P. acnes* [17], in contrast to a separate study of clindamycin monotherapy in which clindamycin-resistant *P. acnes* increased by approximately 1600% versus baseline [18]. Thirdly, fixed-dose combination products may also be more convenient for patients than applying two separate formulations [1, 19]. Together these factors may improve patients' adherence with their treatment, which is a particular problem for adolescent patients, and this in turn will ultimately improve clinical outcomes [20-22]. Additional properties of Clin-RA, such as it being a gel formulation which can be applied once-daily with the fingers and which can be stored at room temperature, may further enhance adherence to this fixed-dose combination [23].

Clin-RA and the combination of adapalene 0.1% and BPO 2.5% both contain a retinoid in addition to an antimicrobial agent and so can effectively treat both inflammatory and non-inflammatory lesions. In contrast, studies have shown that a combination containing clindamycin 1% and BPO 5% is less effective against non-inflammatory lesions since the combination does not contain a retinoid to target the microcomedone [24, 25]. In addition, as mentioned previously, Clin-RA is less irritating than adapalene 0.1%/BPO 2.5%, which may be important in maintaining patient satisfaction and compliance [14]. Furthermore, Clin-RA is likely to be preferred by patients compared with adapalene 0.1%/BPO 2.5% and clindamycin 1%/BPO 5% since it is easy to apply and does not contain BPO which can bleach hair and coloured fabrics.

In conclusion, this pooled analysis of data including over 4500 patients aged 12 years or older from three pivotal phase III studies has confirmed that Clin-RA is well tolerated and an effective treatment against both the inflammatory and non-inflammatory lesions of acne vulgaris, and so should be considered as one of the first-line therapies for mild-to-moderate facial acne. ■

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