Comparison of Micronized Tretinoin Gel 0.05% and Tretinoin Gel Microsphere 0.1% in Young Adolescents With Acne: A Post Hoc Analysis of Efficacy and Tolerability Data

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Acne vulgaris is common in young adolescents. Retinoids are widely used but may be associated with poor tolerability. This post hoc analysis of 483 participants aged 10 to 14 years with mild to moderate acne compared efficacy and tolerability of once-daily treatment with micronized tretinoin gel 0.05%, tretinoin gel microsphere 0.1%, and vehicle over 12 weeks.

In study 1, inflammatory and noninflammatory lesion reduction and treatment success was comparable between tretinoin gel 0.05% and tretinoin gel microsphere 0.1%. Inflammatory (46.3%) and noninflammatory (45.7%) lesion reductions with tretinoin gel 0.05% were significantly greater than vehicle (37.1% and 27.9%, respectively) (both P<.001). In study 2, inflammatory and noninflammatory lesion reductions and treatment success with tretinoin gel 0.05% (30.6%, 39.1%, and 19%, respectively) were significantly greater than vehicle (10.9%, 16.9% [both P<.001], and 4% [P=.008], respectively).

Tretinoin gel 0.05% was significantly better tolerated than tretinoin gel microsphere 0.1% (P<.001); the majority of adverse events (AEs) were mild, occurring in the first 2 weeks. Fourteen percent of participants reported dry skin, 8% skin burning sensation, 5% erythema, and 5% dermatitis exfoliative with tretinoin gel 0.05% compared with 32%, 11%, 23%, and 23%, respectively, with tretinoin gel microsphere 0.1% (all P<.001, except skin burning sensation).

In this secondary analysis of acne in young adolescents aged 10 to 14 years, micronized tretinoin gel 0.05% provided a comparable lesion reduction and treatment success versus tretinoin gel microsphere 0.1%, with a better cutaneous tolerability profile.

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Acne is one of the most common skin disorders in adolescents with a prevalence estimated at 81% to 95% in adolescent boys

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and 79% to 82% in adolescent girls by 16 to 17 years of age.[1] However, acne begins in the prepubertal period when increased amounts of adrenal androgens cause enlargement of the sebaceous glands and increased production of sebum on the face, chest, and back. Clinically diagnosed acne can affect 28% to 61% of children aged 10 to 12 years.[2-4] Few studies have focused on the therapeutic challenges of treating acne in this younger age group.

Successful management of acne includes targeting multiple pathogenic factors and providing treatment regimens that balance sustained efficacy with minimal side effects.[5,6] Mainstays of topical treatment include retinoids and antibacterial agents such as benzoyl peroxide and antibiotics. Topical retinoids affect both comedonal and inflammatory components of acne, presumably because they act to reduce obstruction within the follicle and have some direct anti-inflammatory properties.[7,8]

Within the pediatric population it is especially important for treatment to balance efficacy and tolerability. In this report we provide a detailed analysis of 2 preparations of tretinoin given to young adolescents aged 10 to 14 years. The study population consists of adolescent participants from 2 previously published randomized and controlled clinical trials.[9]

METHODS

Study Design

Individuals with mild to moderate acne who were participants in 2 previously published clinical trials[9] were included in this analysis. The studies evaluated the comparative efficacy and safety of micronized tretinoin gel 0.05% and tretinoin gel microsphere 0.1%. Both were 12-week, multicenter, double-blind, phase 3 studies. Together they enrolled 1537 participants. In study 1, participants were randomized (2:2:1) to receive tretinoin gel 0.05%, tretinoin gel microsphere 0.1%, or vehicle, respectively. In study 2, participants were randomized (1:1) to receive tretinoin gel 0.05% or vehicle.[9]

Study visits were conducted at weeks 1, 2, 4, 8, and 12. At each visit, investigators performed counts of inflammatory (papules, pustules) and noninflammatory (open and closed comedones) lesions. Additionally, they provided a global severity score (0=clear; 1=almost clear; 2=mild; 3=mildly moderate; 4=moderate; 5=severe) to assess treatment success. Adverse events (AEs) also were recorded.

Study Population

Participants in this post hoc analysis were aged 10 to 14 years, of any race and either sex, and presented with mild to moderate acne. They were required to have 15 to 40 inflammatory facial lesions; 30 to 125 noninflammatory facial lesions; and a global severity score of 2 (mild), 3 (mildly moderate), or 4 (moderate). There were no participants with mild acne in study 1.

Exclusion criteria included pregnancy or breastfeeding, presence of other dermatologic conditions (eg, acne conglobata, acne fulminans), specified medications without appropriate washout (eg, corticosteroids or antibiotics on the facial area), use of therapies or treatments with potential to interfere in the interpretation of the study results, and potentially toxic doses of oral vitamin A.[9]

Efficacy Evaluations

Efficacy evaluations included reduction in inflammatory and noninflammatory lesion counts. Treatment success was defined as a global severity score of 0 (clear) or 1 (almost clear) and a minimum 2-grade change from baseline score.

Safety Evaluations

Safety was evaluated through reported AEs. Cutaneous safety (erythema and scaling) and tolerability (itching, skin burning sensation, and stinging) were evaluated by pooling the data from both studies to include all participants aged 10 to 14 years.

RESULTS

Efficacy

In the 2 studies, 483 participants were aged 10 to 14 years and included in this analysis. In study 1, 122 participants were treated with tretinoin gel 0.05%, 115 participants with tretinoin gel microsphere 0.1%, and 62 participants with vehicle. In study 2, 90 participants were treated with tretinoin gel 0.05% and 94 participants with vehicle.

Acne Lesion Counts—In study 1, the reduction in inflammatory and noninflammatory lesions was comparable between micronized tretinoin gel 0.05% and tretinoin gel microsphere 0.1% at week 12 with separation from the vehicle effect after 2 to 4 weeks (Figures 1 and 2). The median percentage reduction in inflammatory and noninflammatory lesions with tretinoin gel 0.05% also was significantly superior to vehicle at week 12 ($P<.001$). Inflammatory lesion counts were reduced by 46.3% and noninflammatory lesion counts by 45.7% compared with 37.1% and 27.9%, respectively, with vehicle (Figure 3).

In study 2, the median percentage reduction in inflammatory and noninflammatory lesions with tretinoin gel 0.05% was significantly superior to vehicle at week 12 ($P<.001$). Inflammatory lesion counts were reduced by 30.6% and noninflammatory

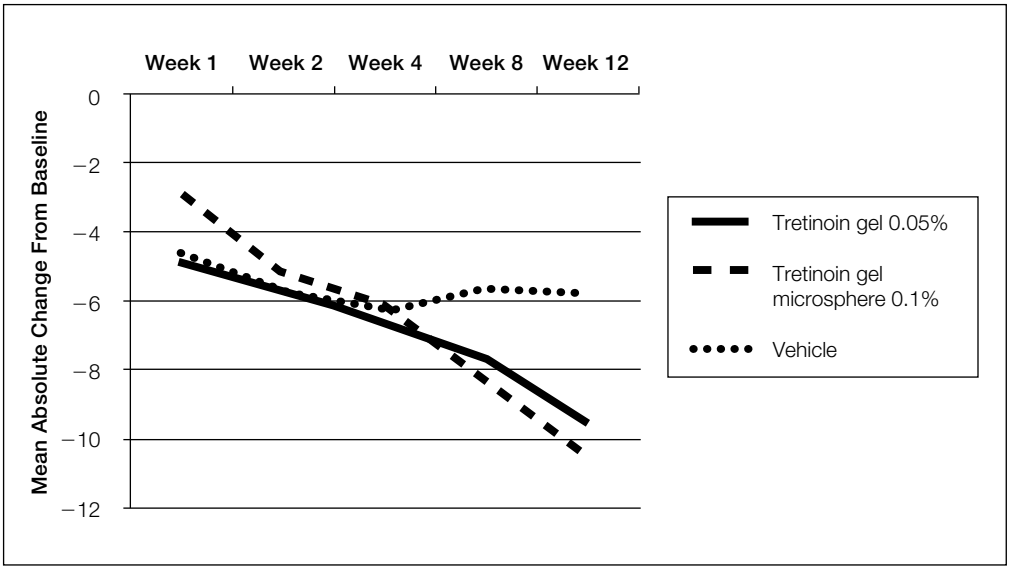

Figure 1. Reduction in inflammatory lesions (study 1) (N=299).

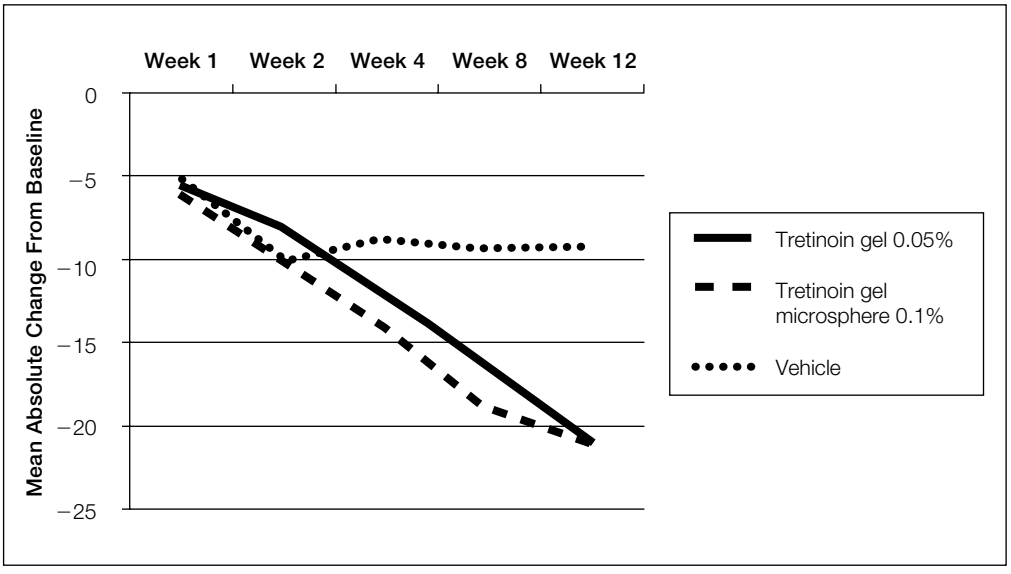

Figure 2. Reduction in noninflammatory lesions (study 1) (N=299).

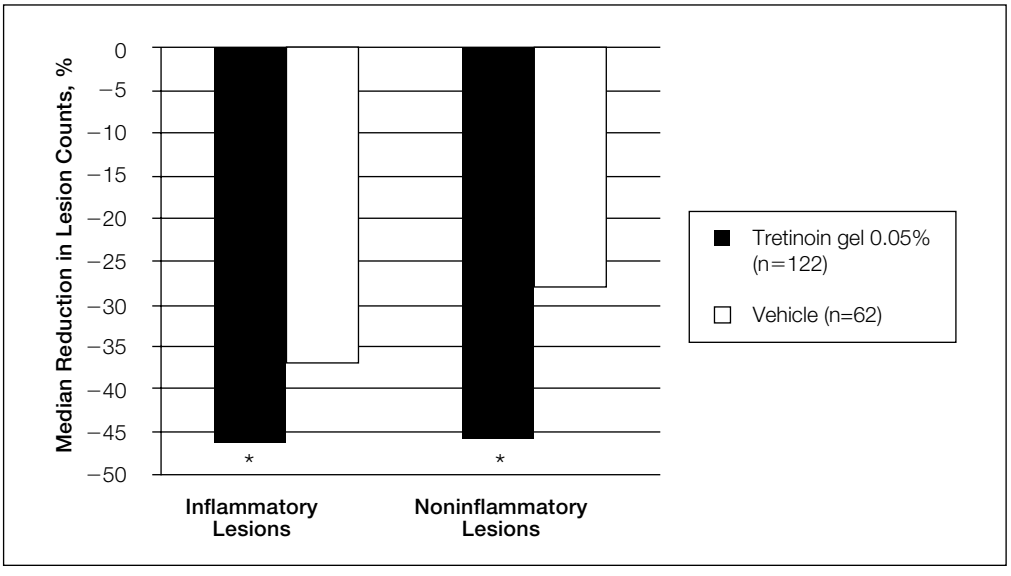

Figure 3. Reduction in inflammatory and noninflammatory lesions at week 12 (study 1)(N=299). Asterisk indicates $P<.001$ versus vehicle.

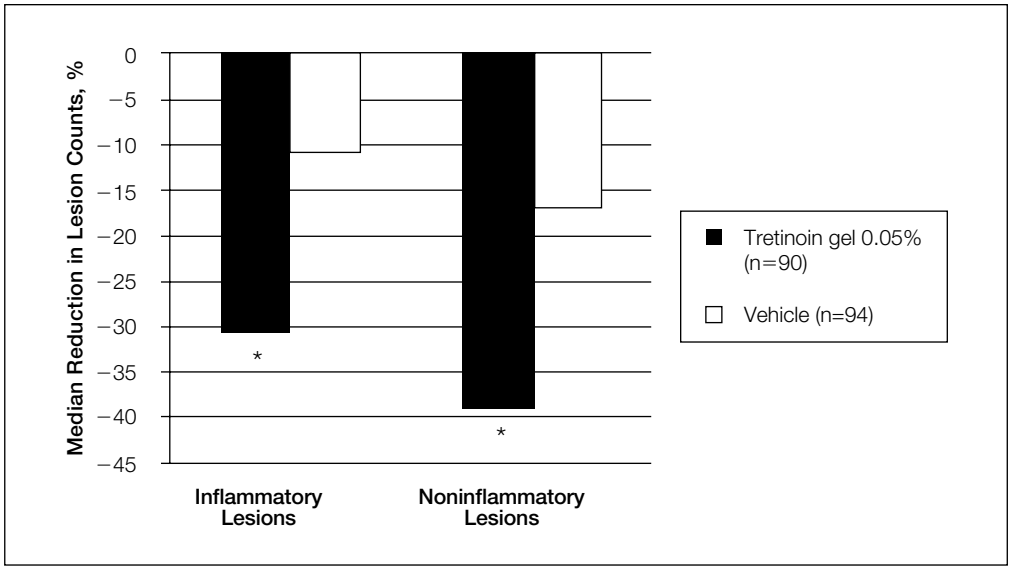

Figure 4. Reduction in inflammatory and noninflammatory lesions at week 12 (study 2) (N=184). Asterisk indicates *P*<.001 versus vehicle.

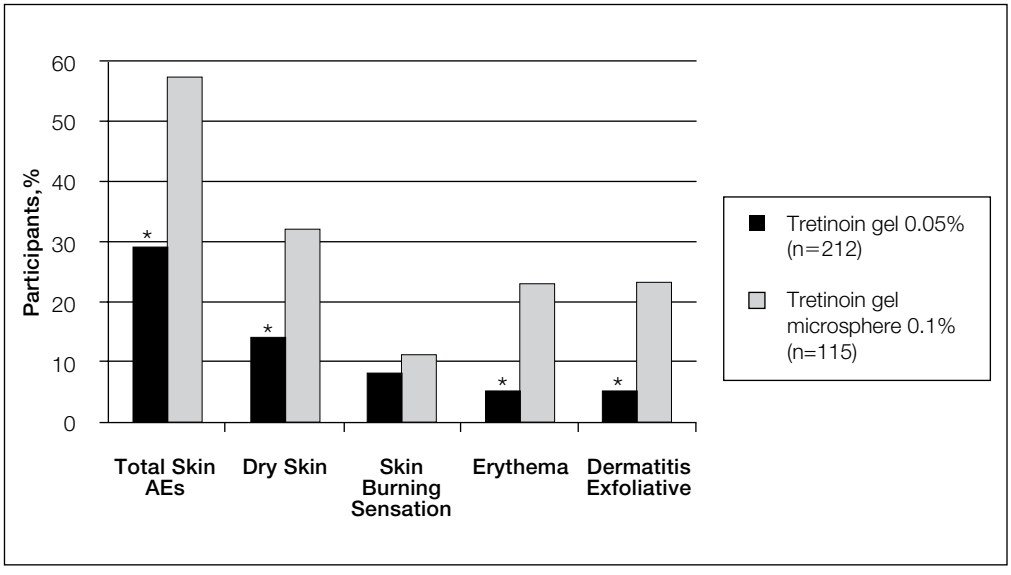

Figure 5. Cutaneous tolerability results (pooled data). Asterisk indicates *P*<.001 versus tretinoin gel microsphere 0.1%. AE indicates adverse event.

lesion counts by 39.1% compared with 10.9% and 16.9%, respectively, with vehicle (Figure 4).

Global Severity Score—In study 1, 18% of participants treated with tretinoin gel 0.05% were clear or almost clear at week 12. Eleven percent of participants were judged as treatment successes based on a global severity score of 0 (clear) or 1 (almost clear) and a minimum 2-grade change from baseline. Ten percent of participants were considered treatment successes in the tretinoin gel microsphere 0.1% group. Results with both retinoid preparations were significantly better than vehicle, with only 2% of participants considered as treatment successes at week 12 (*P*=.021).

In study 2, 19% of participants treated with tretinoin gel 0.05% were judged as treatment successes based on a global severity score of 0 (clear) or 1 (almost clear) and a minimum 2-grade change from baseline compared with 4% with vehicle (*P*=.008).

Safety

Adverse Events—There was 1 serious AE in both active treatment groups and 3 participants (1%) discontinued due to AEs in the tretinoin gel 0.05% group. The number of participants experiencing 1 or more AEs was 52% with tretinoin gel 0.05%, 65% with tretinoin gel microsphere 0.1%, and 28% with vehicle. The incidence of AEs considered possibly,

probably, or related to therapy was 29% with tretinoin gel 0.05%, 55% with tretinoin gel microsphere 0.1%, and 6% with vehicle. All of the reported skin AEs were mild to moderate in severity: 85% were mild with tretinoin gel 0.05%, 65% with tretinoin gel microsphere 0.1%, and 100% with vehicle.

Cutaneous Tolerability Assessments—Overall skin AEs were statistically significantly lower with tretinoin gel 0.05% compared with tretinoin gel microsphere 0.1%; 29% and 57%, respectively, reported skin AEs ($P<.001$). Six percent of participants on vehicle had skin AEs. The most common AEs with tretinoin gel 0.05% were dry skin (14%), skin burning sensation (8%), erythema (5%), and dermatitis exfoliative (5%), and all were significantly lower compared with tretinoin gel microsphere 0.1% with results of 32%, 11%, 23%, and 23%, respectively (all $P<.001$, except skin burning sensation)(Figure 5). The most common skin AEs with vehicle were skin burning sensation (3%) and dry skin (1%). Most of the skin AEs occurred in the first 2 weeks of active treatment (69% and 76%, respectively).

COMMENT

The results of this post hoc analysis suggest that once-daily use of micronized tretinoin gel 0.05% is an effective, safe, well-tolerated therapy for acne in patients aged 10 to 14 years. Currently it is the only retinoid treatment indicated for patients as young as 10 years of age; other products are approved for patients 12 years and older. Reduction in lesion counts and treatment success with tretinoin gel 0.05% was comparable to tretinoin gel microsphere 0.1%. Relative to its vehicle, tretinoin gel 0.05% demonstrated significant superiority in the reduction of inflammatory and noninflammatory lesion counts ($P<.001$ for study 1 and study 2) as well as in an analysis of the dichotomized global severity scores at week 12 (study 1, $P=.021$; study 2, $P=.008$).

An important limitation is that this study was a post hoc analysis of a cohort that was defined retrospectively. Differences in the 2 studies in terms of median percentage reductions in lesion counts and treatment success may be attributed to the differences in participant population; there were no participants with mild acne in study 1.

Retinoid therapy has been associated with irritation, exfoliation, dryness, and scaling, especially during the first 2 to 4 weeks of treatment, which can be an important barrier to continued compliance. Analyses of the pooled study data showed that the incidence of skin-related AEs after treatment with tretinoin gel 0.05% was lower than tretinoin gel microsphere 0.1%.

Overall, this analysis found that micronized tretinoin gel 0.05% appears to be an effective therapy for acne in young adolescents aged 10 to 14 years. The overall efficacy of tretinoin gel 0.05% in this post hoc analysis was comparable to multicenter, double-blind, phase 3 clinical studies. Although the median percentage reductions in lesion counts were slightly lower than previously reported,[9] these participants had a greater number of lesions at baseline compared to the total participant population. The difference in severity of acne also may be a factor in the relative comparative efficacy between micronized tretinoin gel 0.05% and tretinoin gel microsphere 0.1% seen in the 2 separate analyses. In this subpopulation, there was slightly better tolerability with tretinoin gel 0.05% compared to the total study population[9] and more cutaneous side effects with tretinoin gel microsphere 0.1%, suggesting that micronized tretinoin gel 0.05% may be particularly beneficial in an early adolescent acne population in which adherence is more of a problem.[10]

Micronized tretinoin gel 0.05% shows comparable efficacy to tretinoin gel microsphere 0.1% with a lower incidence of skin-related AEs,[9] perhaps because the micronized tretinoin gel 0.05% formulation contained half the concentration of tretinoin versus tretinoin gel microsphere 0.1%. Although not directly compared, the incidence rates observed with tretinoin gel 0.05% in this combined analysis are 50% to 75% lower than those rates reported in the literature for other tretinoin formulations, all containing tretinoin at 0.025%.[11,12] It is possible that the vehicle formulation of tretinoin gel 0.05% plays a role in both the favorable efficacy and tolerability profile. Further investigation of optimized vehicles for better efficacy and tolerability, especially in a younger population with acne, is warranted.

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