

A Double-Blinded, Randomized, Vehicle-Controlled, Multicenter, Parallel-Group Study to Assess the Safety and Efficacy of Tretinoin Gel Microsphere 0.04% in the Treatment of Acne Vulgaris in Adults

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This double-blinded, randomized, vehicle-controlled, multicenter, parallel-group, 12-week, phase 4 study was conducted in adults with mild to moderate acne vulgaris. Of 178 subjects randomized to be treated, 88 subjects (49%) were treated with tretinoin gel microsphere 0.04% and 90 subjects (51%) were treated with vehicle.

Inflammatory lesion counts were statistically significantly reduced at 2 weeks in tretinoin-treated subjects ($P = .0110$), and reductions in total lesion counts also were noted. The reduction in total lesion counts reached statistical significance at week 4 ($P = .0305$); at week 12, mean total, inflammatory, and noninflammatory lesion counts were statistically significantly lower in the tretinoin treatment group versus vehicle group ($P < .05$), and mean percentage reductions in lesion counts were significantly greater in the subjects with

noninflammatory lesions treated with tretinoin compared with vehicle ($P < .05$). Mean percentage reductions in total, inflammatory, and noninflammatory lesion counts were 35.5%, 38.2%, and 33.6%, respectively, at week 12 for the tretinoin treatment group compared with 20.9%, 19.2%, and 20.4%, respectively, for the vehicle group (all $P < .05$). All adverse events were of mild or moderate intensity with the exception of severe skin irritation in one tretinoin-treated subject. At week 12, there were no statistically significant differences between treatment groups for any measured tolerability parameter.

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In the United States, more than 4.5 million patients aged 25 to 44 years are affected by acne, which represents 8% of adults aged 25 to 34 years and 3% of adults aged 35 to 44 years.¹ Women especially may continue to experience acne throughout adulthood, up to and beyond 40 years of age, in some cases¹; prevalence rates of 12% to 41% in women older than 25 years have been reported.^{2,3} Premenstrual acne flares are common.¹

In adults, inflammatory acne is more common than comedonal acne. Also, the location of lesions in adults differ from the usual teenage pattern (ie, face, chest, back) and most commonly affect areas around the mouth, chin, and jawline.¹ Late-onset acne in women may differ from acne that has persisted since adolescence because sebum secretion rates are higher in the latter group.⁴

Although a variety of topical and systemic agents are available, retinoids are the only topical antiacne agents believed to be effective against the microcomedone, which is the precursor lesion of acne.^{5,6} Tretinoin decreases abnormal keratinization, restores normal desquamation of follicular cells, facilitates comedolysis, and decreases the number of microcomedones.⁷ Early formulations of tretinoin tended to cause excessive skin irritation because of both the high concentration of active ingredient and the hydroalcoholic vehicle. Topical formulations with lower concentrations of tretinoin and alternate vehicles are now available, but local skin irritation still may limit their use.⁸

Tretinoin gel microsphere is formulated with spongelike, porous, polymeric microspheres (polyol-prepolymer-2) that encapsulate the active ingredient and serve as a reservoir. Tretinoin is released by the vehicle gradually, which potentially can reduce irritation. The microsphere protects the degradation of tretinoin by peroxide and the degradation of erythromycin by tretinoin, and also

protects tretinoin from photodegradation.⁹ Tretinoin gel microsphere 0.1% and 0.04% markedly decreased noninflammatory lesion counts in vehicle-controlled clinical trials^{10,11} and may result in a faster onset of action in the reduction of comedones compared with adapalene, a synthetic polyaromatic retinoid.¹² Tretinoin gel microsphere 0.1% demonstrated a lower irritation profile compared with tretinoin cream 0.1% in a half-face comparison trial and a cumulative 21-day irritation evaluation.¹¹ Because of the tolerability of the 0.04% formulation, the present study evaluated the safety and efficacy of tretinoin gel microsphere 0.04% compared with vehicle. This is the first study of tretinoin for the treatment of acne in an exclusively adult population.

Materials and Methods

Study Design and Participants—This was a double-blinded, randomized, vehicle-controlled, multicenter, parallel-group, 12-week, phase 4 study conducted in adults with acne vulgaris. The protocol was reviewed by the appropriate institutional review board at each of the 9 participating study sites.

Subjects were between 19 and 45 years of age with mild to moderate acne vulgaris. To qualify for inclusion, each subject had to have between 15 and 80 total facial lesions that consisted of 10 to 40 inflammatory lesions and no more than 2 nodules.

Subjects were instructed to apply tretinoin gel microsphere 0.04% to the face once nightly for 12 consecutive weeks. A facial cleanser and moisturizer were supplied throughout the study period. A sunscreen with sun protection factor 30 was to be used during periods of extended UV exposure. Subjects were instructed not to apply moisturizers or cosmetics to the face on the day of the study evaluation.

Subjects were evaluated for safety and efficacy at baseline and after 2, 4, 8, and 12 weeks of therapy. At each visit, subjects were evaluated for inflammatory lesions (papules and pustules), noninflammatory lesions (open and closed comedones combined), and nodules. Safety evaluations included incidence and severity of adverse events, and signs and symptoms of cutaneous irritation (ie, erythema, peeling, dryness, burning/stinging, and pruritus). Cutaneous irritation was rated on a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe).

The primary efficacy end point was the percentage change in total lesion counts from baseline to week 12. In instances where an efficacy evaluation was missing, the last available efficacy assessment replaced the missing value. If no postbaseline data were available, the baseline value was used.

Secondary end points included the change from baseline and percentage change from baseline in inflammatory and noninflammatory lesions at weeks 2, 4, and 8.

At week 12, the investigator global assessment and subject self-assessment also were completed. Investigators rated each subject's acne as cleared (0 lesions), almost cleared (90% improvement), marked improvement (75% improvement), moderate improvement (50% improvement), mild improvement (25% improvement), no change, and worsening. For the self-assessment, subjects were asked, "How would you rate your acne improvement since you started this study?" Ratings were based on a 5-point scale (1=much improved, 2=somewhat improved, 3=not improved, 4=worse, 5=much worse).

Statistical Analysis—All statistical tests were 2-tailed and performed at a significance level of 5%, except for tests of interaction, which used an α level of 10%. Summary statistics of continuous variables included the number of nonmissing values and the mean, median, SD, and minimum and maximum values. The SAS Institute Inc general linear model procedure using type 3 sums of squares was used to perform comparisons among study treatment groups using continuous response variables. Statistical methods for assessing treatment differences were based on SAS® version 8.2 statistical software for all statistical analyses. The Cochran-Mantel-Haenszel (CMH) test, using the row mean score test statistic with modified ridit scores and stratified by center, was used to test for treatment group differences in the investigator global assessment of treatment response and subject self-assessments.¹³

The primary population for efficacy evaluation was the intent-to-treat population, comprised of all randomized subjects who had at least a baseline efficacy evaluation and who were analyzed for efficacy. If a subject lacked secondary efficacy data (eg, investigator global assessment), a response of "no change" was assumed. A transformation of the lesion count data was required to accommodate zero counts in the statistical analyses. If the baseline lesion count was zero, the statistical analyses were carried out with 0.1 lesion added to each subject's lesion count at baseline and at all postbaseline values.

All randomized subjects who received any study medication were included in the safety population. Adverse events were coded according to the Medical Dictionary for Regulatory Activities. Treatment comparisons for the change from baseline to each visit in cutaneous irritation variables used the CMH row mean score test statistic with modified ridit scores stratified by the investigator.

Concomitant medications were coded using the World Health Organization drug glossary. The CMH test, using the row mean score test statistic with modified ridit scores, was used to evaluate treatment differences in concurrent topical medications at weeks 2, 4, 8, and 12.

Results

Study Population—One hundred seventy-eight subjects were randomized to be treated; 88 subjects (49%) were treated with tretinoin gel microsphere 0.04% and 90 subjects (51%) were treated with vehicle. The demographic characteristics of the treatment groups were not significantly different, though the tretinoin treatment group tended to be younger than the vehicle group by approximately 2 years (mean age, 26.7 years and 29.0 years, respectively). Most subjects (82%) were women, and approximately 60% were white, 25% were black, and 13% were Hispanic (the remaining 2% were Other). Treatment groups were balanced with respect to baseline distributions of individual lesion counts (mean total, 42), and mean papule and pustule counts were not statistically significantly different between treatment groups (overall mean, 14.0 papules and 2.6 pustules).

Of the 178 randomized study subjects, 42 subjects (24%) discontinued therapy prior to study completion (20 subjects in the tretinoin treatment group; 22 subjects in the vehicle group). The most common reason for discontinuation was lost to follow-up (20 subjects). Four subjects in the tretinoin treatment group discontinued for adverse events, and one vehicle-treated subject discontinued because of treatment failure.

Concomitant medications used by more than 5% of subjects in the total study population were oral contraceptives (16%), multivitamins (6%), analgesics and antipyretics (16%), and antidepressants (5%).

Safety—Thirty-six percent of subjects treated with tretinoin and 29% of vehicle-treated subjects reported at least one adverse event. The most frequent adverse events were of skin and subcutaneous tissue body system and were present in 24% of tretinoin-treated subjects and 4% of vehicle-treated subjects. All adverse events were of mild or moderate intensity with the exception of severe skin irritation in one tretinoin-treated subject. There were no serious adverse events and no reported deaths. Only cutaneous events were judged to be related to treatment (ie, dryness, erythema, localized exfoliation, pruritus, skin irritation).

Tolerability—At baseline, the 2 treatment groups were comparable in the proportions of subjects with no, mild, or moderate erythema, peeling, dryness,

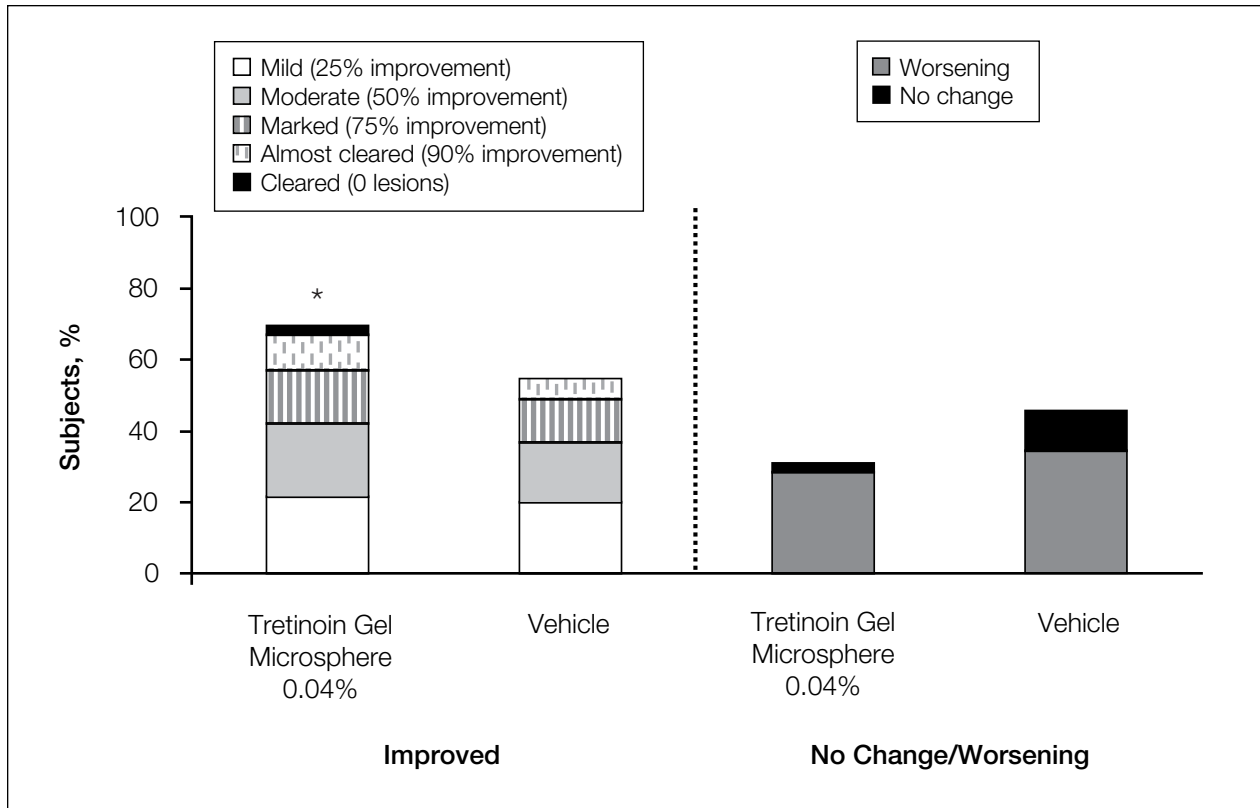


Figure 1. Investigator global assessment of acne improvement at week 12 (tretinoin gel microsphere 0.04%, n=88; vehicle, n=90). Asterisk indicates $P=.005$.

burning/stinging, and pruritus. Overall, approximately 90% of subjects reported none or mild grades for each of the tolerability variables at baseline. At week 12, there were no statistically significant differences between treatment groups for any measured tolerability parameter.

Efficacy—At week 12, mean total, inflammatory, and noninflammatory lesion counts were statistically significantly lower in the tretinoin treatment group versus vehicle group ($P<.05$), and mean percentage reductions in lesion counts were significantly greater in the subjects with noninflammatory lesions treated with tretinoin versus vehicle ($P<.05$). Mean percentage reductions in total, inflammatory, and non-inflammatory lesion counts were 35.5% ($P=.0073$), 38.2% ($P=.0081$), and 33.6% ($P=.0368$), respectively, at week 12 for the tretinoin treatment group compared with 20.9%, 19.2%, and 20.4%, respectively, for the vehicle group. Reductions in total lesion counts were noted at 2 weeks in tretinoin-treated subjects and reached statistical significance at week 4 ($P=.0305$). Reductions in inflammatory lesion counts were significantly different at week 2 in tretinoin-treated subjects ($P=.0110$); this efficacy gap continued to widen over the next 10 weeks of treatment.

Global Evaluation of Treatment Response—The results of the investigator global assessment of clinical response for week 12 are presented in Figure 1. At the end of the study, 2 tretinoin-treated subjects were rated as cleared by the investigator, 9 subjects were considered almost cleared (90% improvement), and 2 subjects were considered to have worsened. Nearly half of the subjects treated with tretinoin achieved at least moderate improvement ($\geq 50\%$ improvement) ($P=.005$). Approximately one third of subjects treated with vehicle achieved a rating of at least moderate improvement, 10 subjects worsened, and no subjects were considered cleared of lesions.

Subject Self-assessment—Subject self-assessment responses to the question, “How would you rate your acne improvement since you started this study?” are shown in Figure 2. Significantly more subjects treated with tretinoin rated their acne as much improved compared with vehicle-treated subjects (23 subjects [26%] vs 13 subjects [14%], respectively; $P=.0218$). Sixty-five percent of tretinoin-treated subjects considered their acne to be improved compared with 50% of vehicle-treated subjects.

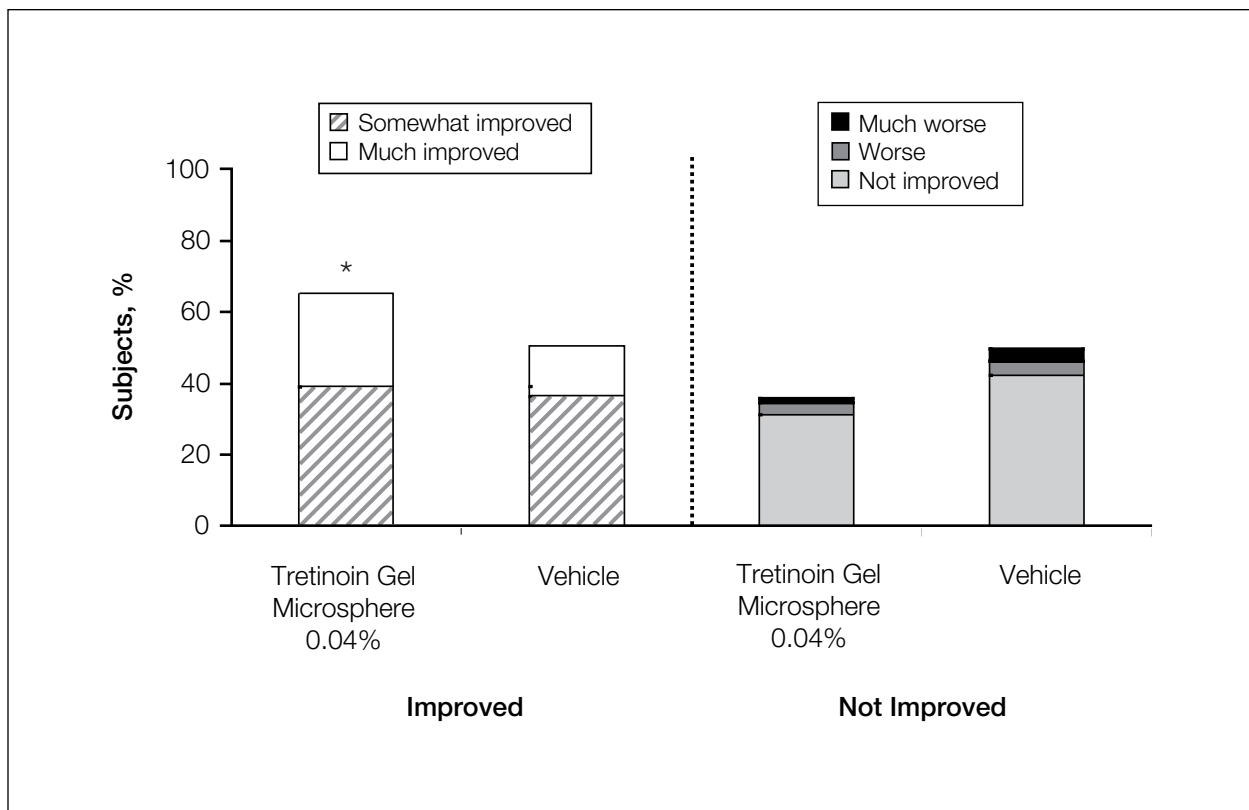


Figure 2. Subject self-assessment of acne improvement at week 12 (tretinoin gel microsphere 0.04%, n=88; vehicle, n=90). Asterisk indicates $P=.0218$.

Comment

This is the first study of tretinoin for the treatment of acne in an exclusively adult population. In this study population consisting primarily of women, tretinoin gel microsphere 0.04% used once daily had pronounced and early effects. Statistically significant improvement in inflammatory lesions occurred as early as week 2 in tretinoin-treated subjects ($P=.0110$), and improvement continued throughout the study. Subjects treated with tretinoin achieved statistically significant improvement in their acne compared to vehicle in total ($P=.0073$), inflammatory ($P=.0081$), and noninflammatory ($P=.0368$) lesion counts after 12 weeks of treatment. Adverse event profiles were comparable, with the exception of skin and subcutaneous tissue body system adverse events, which occurred more frequently in the tretinoin treatment group. Cutaneous irritation in the tretinoin-treated group peaked within the first 3 weeks of treatment and was no different than the vehicle-treated group by the end of the study.

The antiproliferative activity of tretinoin is well-known—tretinoin decreases abnormal keratinization, restores normal desquamation of follicular cells, facilitates comedolysis, and decreases the number of microcomedones⁷—but its efficacy for

the treatment of inflammatory lesions often is not fully appreciated. Inflammatory acne is a result of a continuing immune response to the normal follicular bacterium, *Propionibacterium acnes*, which stimulates inflammation by producing proinflammatory mediators that diffuse through the follicle wall. Variations in individual immune responses to *P acnes* may explain variations in acne severity—the antibody and cellular responses to the bacterium are proportional to the degree of inflammatory acne.¹⁰

One hypothesis suggests that anti-inflammatory effects of tretinoin are mediated through regulation of toll-like receptors (TLRs).¹⁴ Two effects are postulated: one pathway specifically affecting TLR2 and CD14 cells, and one involving the overall TLR signaling pathway. In vitro studies of primary human monocytes showed that treatment with tretinoin led to the down-regulation of TLR2 and CD14 messenger RNA, and decreased the cell surface expression of TLR2 and CD14, resulting in anti-inflammatory activity.¹⁴ Regulation of these pathways is important because TLR2 and its co-receptor CD14 are expressed in acne lesions and activated by *P acnes*. Recently it has been shown that *P acnes* binds to the TLR on monocytes and

neutrophils.¹⁴ Binding of the TLR leads to the production of multiple proinflammatory cytokines, including interleukins 12 and 8, and tumor necrosis factor. These molecular effects of tretinoin on TLR2 and CD14 may explain the efficacy of tretinoin gel microsphere 0.04% on inflammatory acne lesions in this study.

Conclusion

Tretinoin gel microsphere 0.04% used once daily was effective for the treatment of acne in a largely female adult population. Statistically significant reductions in inflammatory lesions were noted after only 2 weeks of treatment ($P=.0110$) and continued throughout the 12-week study, and noninflammatory lesions also improved as expected. Tretinoin gel microsphere 0.04% was equally effective for the treatment of inflammatory and noninflammatory acne in adults. Scientific evidence of the ability of tretinoin to down-regulate the expression of TLR2 confirms the intrinsic anti-inflammatory properties of the drug, which makes it an excellent treatment choice for adults with acne.

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