Double-blind, Randomized, Prospective Trial Comparing a Lipohydroxy Acid Cream With Tretinoin Cream for Acne Vulgaris

E.M. Graber, MD; D.M. Thiboutot, MD; S. Seité, PhD; A. Rougier, PhD; A.R. Shalita, MD

New topical treatments for acne vulgaris are needed for patients who are intolerant of current treatments. Salicylic acid (SA) is an over-the-counter antiacne treatment, and tretinoin is a commonly used prescription antiacne cream. The authors sought to compare efficacy and tolerance of a formula containing SA and a lipophilic derivative of SA (lipohydroxy acid [LHA]) versus a tretinoin cream in participants with mild acne vulgaris. Primarily, the authors wanted to establish equivalent efficacy between these 2 creams. The authors conducted a randomized, double-blind, prospective trial enrolling 85 participants with mild to moderate facial acne. All participants had less than 10 inflammatory lesions and 20 to 40 comedones. Participants were randomized to receive either cream containing SA plus LHA twice a day or tretinoin once daily for 87 days. Efficacy and tolerability were assessed by both the participants and the investigator at days 0, 28, 56, and 87. At the conclusion of the study, participants also completed a questionnaire with regards to efficacy and the cosmetic properties of their given cream. Seventy-three participants completed the study, of which 37 used SA/LHA and 36 used tretinoin. With the exception of pustules ($P=.10$), all lesion types (open comedones, closed comedones, and papules) decreased significantly with both creams from day 0 to day 87 ($P<.0001$, $P<.0001$, $P=.0001$, respectively). This decrease did not significantly vary between the 2 treatment groups. However, the decreases in lesions were not similar enough to deem the 2 treatments equivalent. The participants graded both treatments acceptable and well tolerated although there was more desquamation at day 28 in the group receiving tretinoin ($P=.002$). The small sample size was a limitation of this study. In addition, 12 of 85 (14%) participants were lost to follow-up. The SA/LHA cream and tretinoin cream were both effective in reducing acne vulgaris. However, they were not found to be equivalent. Nevertheless, this study suggests that the SA/LHA formulation could be a treatment option to consider in patients with acne vulgaris who are intolerant to tretinoin.

Dr. Graber is Staff Dermatologist, SkinCare Physicians, Chestnut Hill, Massachusetts. Dr. Thiboutot is Professor of Dermatology, Department of Dermatology, Pennsylvania State University College of Medicine, Milton S. Hershey Medical Center, Hershey. Dr. Seité is Clinical Studies Manager, and Dr. Rougier is International Scientific Director, both at La Roche-Posay Pharmaceutical Laboratories, Asnières, France. Dr. Shalita is Professor and Chairman, Department of Dermatology, State University of New York Downstate Medical Center, Brooklyn, New York.

Dr. Thiboutot is a consultant for Allergan, Inc; Galderma Laboratories, LP; and Johnson & Johnson Services, Inc. Dr. Shalita has an equity position in Johnson & Johnson Services, Inc, and has an ongoing relationship with Ortho Dermatologics.

Correspondence: Emmy M. Graber, MD, SkinCare Physicians, 1244 Boylston St, Chestnut Hill, MA, 02467 (egraber@skincarephysicians.net).

Acne vulgaris is an exceedingly common condition affecting both teenagers and adults. Treatments include a variety of prescriptions and over-the-counter (OTC) antiacne creams. While many studies have been conducted proving the efficacy of antiacne creams, few head-to-head trials exist comparing an OTC medicine to a prescription medicine.

Tretinoin (all-*trans*-retinoic acid), a topical vitamin A derivative, was first evaluated for the treatment of icthyosis in 1962. Seven years later, its utility in treating acne was unveiled by Kligman.[1] Today, several strengths (0.025%, 0.05%, and 0.1%) of tretinoin are available by prescription and in different formulations (cream, gel, or solution). Tretinoin exerts its effect against acne in a number of ways. It increases the rate of keratinocyte migration through the epidermis and decreases the cohesiveness of keratinocytes. Both of these properties prevent the formation of comedones.[2] Tretinoin has also been shown to decrease inflammation by downregulating toll-like receptor 2, a receptor known to stimulate proinflammatory cytokines.[3] Because of its multiple mechanisms of action, tretinoin is effective in treating both comedones and inflammatory lesions.[4]

Shown to be an effective treatment for acne, OTC salicylic acid (SA) is found in different formulations and strengths ranging from 0.5% to 2.0%.[5] A lipophilic hydroxy acid derivative of SA, 2-hydroxy 5-octanoyl benzoic acid, has comedolytic, anti-inflammatory, and antibacterial properties.[5]

METHODS

Eighty-five participants (25 men, 60 women) afflicted with mild to moderate facial acne vulgaris were enrolled in the trial. To be included in the trial, participants had to be at least 18 years old, have 20 to 40 comedones, and less than 10 inflammatory lesions. Participants who were pregnant or breast-feeding, had serious or progressive skin conditions, were planning on prolonged sun exposure, and those with facial skin conditions other than acne were excluded from the study.

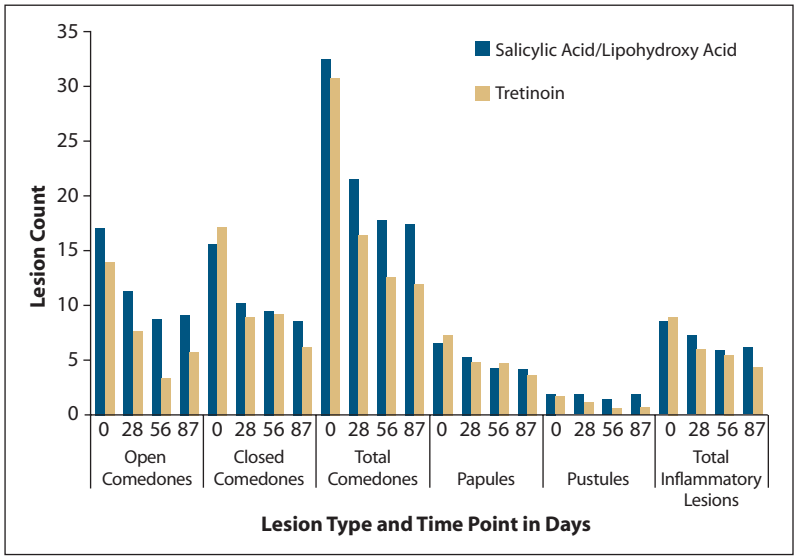
Participants were randomized to use either a formula containing SA 1.5% and lipohydroxy acid (LHA) 0.3% twice a day or tretinoin 0.05% cream once nightly and were instructed to evenly apply a pea-sized amount of their given cream to the face. The SA/LHA formula is a cream containing aqua/water; di-c12-13 alkyl malate; cyclohexasiloxane; propylene glycol; aluminum starch octenylsuccinate; PEG-100 stearate; glyceryl stearate; salicylic acid; cetyl alcohol; PEG-4 dilaurate; PEG-4 laurate; zinc pyrrolidone carboxylate; sodium hydroxide; capryloyl salicylic acid; xanthan gum; acrylates/C10-30 alkyl acrylate cross-polymer; iodopropynyl butylcarbamate; and parfum/fragrance. Tretinoin cream is a water-in-oil emulsion that contains tretinoin; butylated hydroxytoluene; citric acid monohydrate; dimethicone 50 cs; edetate disodium; fragrance; hydroxyoctacosanyl hydroxystearate; light mineral oil; methoxy PEG-22/dodecyl glycol copolymer; methylparaben; PEG-45/dodecyl glycol copolymer; purified water; quaternium-15; stearoxytrimethylsilane and stearyl alcohol; and sorbitol solution.

A blinded investigator evaluated the participants at days 0, 28, 56, and 87. At each visit, the blinded investigator counted the number of each type of acne lesion including open comedones, closed comedones, papules, and pustules. Lesions on the nasal pyramid were not counted. For each follow-up time point, the change in the number of acne lesions from baseline was determined. The average change at each time point was compared among the 2 treatment groups using a Student *t*-test. Focus was placed on the average change from baseline to day 87 of treatment since this change encompassed the entire time that a completed participant was on the treatment. To test for differences between treatments over the entire period of the study, analysis of variance for repeated measures was conducted, modeling the correlation between the repeated measures.

The investigator also graded facial sensitivity by assessing erythema and desquamation on a 4-point scale (absent, light, moderate, or severe). Participants also graded their facial sensitivity at each visit by rating pruritus, stinging sensation, and burning sensation on a 4-point scale (absent, light, moderate, or severe). At each visit, the investigator graded overall subjective efficacy as zero, fair, good, or excellent, and participants graded the acceptability of the cream on this same scale. For each time point, comparisons were made using a Pearson chi-square test due to the categorical nature of facial sensitivity grades, overall subjective efficacy, and acceptability ratings. At day 87, participants completed a questionnaire in which they graded the product's effect and tolerability. The questionnaire responses (at day 87) were also compared among treatment groups using a Pearson chi-square test. The statistical analysis will be performed on the intent-to-treat population, which includes all randomized participants regardless of their adherence and length of study follow-up. A significance level of $P<.05$ will indicate statistical significance.

RESULTS

Eighty-five participants (25 men, 60 women) were enrolled in the study and 73 participants completed the study, of which 37 used SA/LHA and 36 used tretinoin. Five participants that had been given tretinoin and



Mean lesion count at days 0, 28, 56, and 87 (salicylic acid/lipohydroxy acid n=37, tretinoin n=36). Treatments were initiated at day 0 and stopped at day 87.

7 participants given SA/LHA withdrew from the study. The average age of the participants was not significantly different (P=.60) between the 2 groups. The mean (SD) age of those receiving SA/LHA was 28.1 (9.7) years and those receiving tretinoin was 27.2 (7.5) years. At the baseline visit (day 0), the number of comedones, inflammatory lesions, and the degree of facial sensitivity as assessed by both the investigator and the participants did not differ significantly between the 2 groups.

At day 28, the number of comedones and the number of inflammatory lesions did not significantly differ between the 2 groups (P=.15, P=.17, respectively). Both groups had a decrease in the number of lesions between day 0 and day 28 but the decrease was not significantly different between the 2 groups. However, the change in lesions between the 2 groups was not small enough to declare equivalence because the 95% confidence interval centered on the observed difference did not lie entirely between the predefined intervals of 15%. At day 28, investigator-rated desquamation was more frequent with tretinoin than with SA/LHA (P=.002). Investigator-rated efficacy at day 28 was not different between the 2 groups (P=.12). However, 51% of participants treated with tretinoin were graded as having a good or excellent efficacy, whereas only 37% in the SA/LHA group were rated this way. The acceptability rated by the participants was mostly good with both groups and did not significantly differ (P=.27) between the 2 treatments.

After 56 days of treatment, the number of open comedones was significantly lower in participants receiving tretinoin than in participants receiving SA/LHA (P=.01). There was no significant difference between the 2 groups for closed comedones, total comedones, papules, pustules, or total inflammatory lesions. However, the 2 treatments could not be considered to be equivalent. At day 56, the investigator and the participants had similar ratings of facial sensitivity in both treatment groups. Desquamation was no longer more frequently associated with tretinoin (as it had been at day 28). The mean efficacy rating and acceptability rating did not significantly differ (P=.69, P=.33) between the 2 groups.

When counting lesions at day 87, the number of total comedones was significantly less in the tretinoin group (P=.04). The number of closed comedones, open comedones, papules, pustules, and total inflammatory lesions was reduced in both treatment groups at day 87 and the difference between the 2 groups was not significant. At day 87, the investigator and the participants had similar ratings of facial sensitivity in both treatment groups. Efficacy was rated good or excellent in 80% of cases with tretinoin cream versus in 60% with the SA/LHA cream. This difference was statistically significant (P=.049). Acceptability was roughly the same (P=.33) between the 2 groups. Formula acceptability was rated good or excellent in 70% of participants using SA/LHA cream and in 80% of participants using tretinoin cream.

All lesions (except pustules) decreased significantly in both groups from day 0 to day 87 (Figure). However, these variations, according to the analysis of variance for repeated measurement, did not globally differ between the 2 treatment groups when comparing among all visits. Between days 0 and 87, the decrease in total comedones was more important with tretinoin (−62.7%) than with SA/LHA formula (−48.9%), but the difference was not significant (P=.06). There was a greater decrease in total inflammatory lesions with SA/LHA formula (−26.8%) than with tretinoin (−19.0%), but the difference was not significant (P=.39). Again, the change in lesions between the 2 groups was not small enough to declare equivalence (using a 15% equivalence range).

When looking at the results of the questionnaire, the texture was qualified to be very pleasant by 57% of the participants using SA/LHA formula and by only 32% of the participants using the tretinoin cream. There was no significant difference between the 2 products with regards to product penetration, ease of application, ease of removal, stickiness, freshness, or product fragrance. On the questionnaire, the participants rated no difference between the efficacies of the 2 tested creams.

DISCUSSION

The main measure of this study was to compare the variance in the decrease of lesions from day 0 to day 87 between the group using SA/LHA cream and the group using tretinoin cream. While both groups had a significant decrease in all lesion types (except pustules) at day 87 from day 0, the reduction was not significantly different between the 2 groups. On the other hand, the reduction was also not similar enough between the 2 treatment groups to deem them equivalent. In other words, both creams worked to reduce acne but no conclusion could be made that they are either equivalent or dissimilar in their efficacy.

At the incremental follow-up visits, some differences could be detected in each treatment group. At day 28, tretinoin caused significantly more desquamation than SA/LHA. This is important to note as any early tolerability issues could prevent the participant from continued use of the medication. Medication compliance is critical for successfully treating acne vulgaris. In addition, teenagers, who are most commonly afflicted with acne, tend to have poor compliance. If a medication is not tolerable, inadequate compliance will result, in turn making even the best treatment ineffective. On the questionnaire that was completed at the end of the trial, participants rated the texture of SA/LHA formula to be significantly more pleasant than the texture of tretinoin cream ($P=.04$).

Open comedones were more significantly reduced at day 56 in those receiving tretinoin than in those using SA/LHA formula. The total number of comedones was also reduced more significantly in the tretinoin group at day 87. In this study, a midstrength tretinoin (0.05%) was compared to a mild strength of SA (1.5%) and derivative (0.3% LHA) association. Perhaps it would have been a fairer comparison to test the low-strength tretinoin (0.025%) against the SA/LHA formula. It was also interesting to note that the SA/LHA formula had been previously evaluated alone or as a complement of tretinoin in acne treatment (eg, apply each cream one evening out of 2), allowing a similar efficacy than tretinoin alone (every evening) and a reduction of the signs of intolerance.[5]

The small to moderate sample size was a limitation of this study. It would be valuable to see if a larger study produced more significant results. The gender and average age of participants in this study may have also skewed the results. The mean age of participants in this study was 28.1 and 27.2 years, respectively. However, the group most commonly afflicted with acne, teenagers, is much younger. Additionally, many more women were enrolled in this study than men (60 women versus 25 men). Hormones play a large role in the pathogenesis of acne in adult women. Hormones may also influence acne in the teenage population, although hormonally directed treatments seem to be especially effective in the adult female population, indicating a hormonal pathogenesis in this age group. Given that the participants in this study were mainly adult females, their acne may have been strongly driven by a hormonal influence. Neither topical SA associated with one of its derivative or tretinoin are helpful in curtailing the hormonal effect on adult acne. Limiting the age of enrollment to the teenage population may have given more authentic results. By including only younger participants, these topical treatments may have imparted a more significant effect since the hormonal influence is not as domineering in this group with acne.

Despite its shortcomings, this study provides useful information for several reasons. It is important to know the efficacy of OTC remedies compared to prescription medications for acne, as a prescription is not often a feasible option for patients. In some underserved areas, it is not possible for a patient to see a physician to obtain a prescription. With trying economic times, more patients are becoming uninsured or cannot afford insurance copayments. The costs of OTC SA formulations are generally much less costly than prescription creams (negating any insurance coverage). It is helpful to know that economical OTC medicines can be beneficial to those unable to see a physician or pay for a prescription medicine.

Overall, both creams significantly reduced open comedones, closed comedones, and papules after 87 days of treatment. At the end of treatment, the efficacy of the 2 creams was not significantly different. However, they were not similar enough to judge them as having equivalent efficacy. Nevertheless, these results suggest that the SA/LHA formulation could be a treatment option to consider in patients with mild to moderate acne vulgaris who are intolerant to tretinoin.

REFERENCES

1. Kligman AM, Fulton JE Jr, Plewig G. Topical vitamin A acid in acne vulgaris. *Arch Dermatol.* 1969;99:469-476.
2. Lavker RM, Leyden JJ, Thorne EG. An ultrastructural study of the effects of topical tretinoin on microcomedones. *Clin Ther.* 1992;14:773-780.
3. Liu PT, Krutzik SR, Kim J, et al. Cutting edge: all-*trans* retinoic acid down-regulates TLR2 expression and function. *J Immunol.* 2005;174:2467-2470.
4. Leyden JJ, Shalita A, Thiboutot D, et al. Topical retinoids in inflammatory acne: a retrospective, investigator-blinded, vehicle-controlled, photographic assessment. *Clin Ther.* 2005;27:216-224.
5. Kligman AM. A comparative evaluation of a novel low-strength salicylic acid cream and glycolic acid products on human skin. *Cosmet Dermatol.* 1997:10(suppl):S11-S15.