

Tretinoin Microsphere Gel Pump 0.04% Versus Tazarotene Cream 0.05% in the Treatment of Mild-to-Moderate Facial Acne Vulgaris

Leon H. Kircik MD FAAD

Mount Sinai School of Medicine, New York, NY
Indiana University, Indianapolis, IN
Physicians Skin Care, PLLC, Louisville, KY

ABSTRACT

This 12-week, single-center, investigator-blinded, randomized, parallel-design study assessed the safety and efficacy of tretinoin microsphere gel 0.04% delivered by pump (TMG PUMP) to tazarotene cream 0.05% (TAZ) in mild-to-moderate facial acne vulgaris. Efficacy measurements included investigator global assessment (IGA), lesion counts, and subject self-assessment of acne signs and symptoms. Efficacy was generally comparable between treatment groups, although TMG PUMP provided more rapid results in several parameters. IGA showed a more rapid mean change from baseline at week 4 in the TMG PUMP group (-0.18 versus -0.05 in the TAZ subjects). TMG PUMP yielded more rapid improvement in papules. At week 4, the mean percentage change from baseline in open comedones was statistically significant at -64% in the TMG PUMP group ($P=0.0039$, within group) versus -19% in the TAZ group (not statistically significant within the group; $P=0.1875$). Skin dryness, peeling and pruritus were significantly less in the TMG PUMP group as early as week 4. Adverse events related to study treatment were rare in both groups and all resolved upon discontinuation of study medication.

INTRODUCTION

Acne is characterized by a variable mixture of lesions: non-inflammatory (open and closed comedones) and inflammatory (papules, pustules, nodules and cysts) in different stages of development as well as their precursor lesion, the microcomedone.

Topical retinoids are used in the management of acne to normalize desquamation of the follicular epithelium in the infundibulum of the pilosebaceous unit by decreasing the cohesiveness of keratinocytes and facilitating extrusion of microcomedones.^{1,3} They reduce the development of new microcomedones and consequently the formation of new inflammatory and non-inflammatory lesions.^{2,4} The normalization of the follicular microenvironment by topical retinoids also renders it less hospitable to the proliferation of *Propionibacterium acnes*.¹

Topical retinoids bind to specific receptors and are taken up into the cell, where they influence gene transcription in pathways involving cellular proliferation and differentiation inflammation, immunomediation and sebum production.⁵ Topical retinoids diminish production of keratohyalin granules by follicular keratinocytes.⁷ Currently available topical retinoids are tretinoin, adapalene and tazarotene, which are marketed in a wide variety of vehicles and delivery systems.

Tretinoin (all-trans retinoic acid) was the first topical retinoid to be approved in the United States (U.S.). It has strong anti-

comedogenic and comedolytic activity, as well as indirect antimicrobial activity, through its ability to alter the follicular environment. Its ability to reduce the numbers of non-inflammatory lesions prevents the progression to inflammatory lesions, in addition to direct anti-inflammatory activity mediated through down regulation of Toll-like receptor-2 (TLR-2).²

Tazarotene, originally indicated for the treatment of plaque psoriasis, was developed to have a more rigid conformational structure so as to make it more receptor-selective and to improve its tolerability.⁸ It has been suggested that tazarotene is the most potent and anti-comedogenic retinoid but also one of the least tolerable in terms of signs and symptoms of cutaneous irritation ("retinoid dermatitis").²

Whereas, topical retinoids were formerly used in patients with predominantly non-inflammatory lesions, they are now considered applicable for initial treatment of both comedonal and inflammatory lesions. It is now widely recommended that topical retinoids be included early in the treatment of most patients with acne. For mild acne, retinoids with or without benzoyl peroxide may be sufficient as monotherapy. This combination is also reported to be the preferred maintenance therapy.^{4,8} The ability of topical retinoids to inhibit the formation of new microcomedones can help break the cycle of acne.⁸

This recent pilot study compared the efficacy and safety of two different topical retinoids in the treatment of mild-to-moderate facial acne vulgaris.

METHODS**Study Design**

This was a 12-week, single-center, investigator-blinded, randomized, parallel-design study that included a total of 40 patients. Inclusion criteria was defined as outpatients ≥ 12 years of age with facial acne vulgaris characterized by 15–60 inflammatory lesions, 10–100 non-inflammatory lesions, ≤ 2 facial nodules and stable disease. Female patients of childbearing age were required to have a negative pregnancy test, and sexually active subjects agreed to practice a reliable method of contraception for the study's duration.

Study Treatments

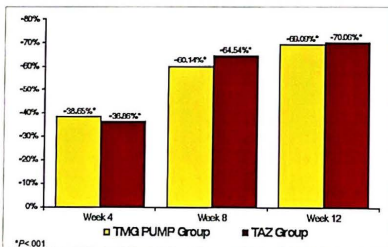
Washout periods prior to the baseline visit were required as follows: topical acne or anti-inflammatory medications on face (14 days), over-the-counter (OTC) acne products (seven days) systemic medications for acne, such as antibiotics or corticosteroids (30 days), oral isotretinoin (90 days) and facial cosmetic procedures (14 days). Study subjects were instructed to apply a pea-size amount of study medication diffusely in a thin layer to their face in the evenings only and to use sunscreen if sun avoidance was impossible.

Efficacy Assessments

Primary efficacy variables were investigator assessments of non-inflammatory lesions (open and closed comedones, total), inflammatory lesions (papules, pustules, nodules, total) and total lesions. Secondary efficacy variables included investigator global assessments (IGA) of acne severity and disease signs and symptoms. Subject assessments of severity of pruritus and burning since the last visit was assessed on a 6-point scale ranging from 0=absent to 5=severe.

Post-inflammatory hyperpigmentation severity was scored on a 6-point scale ranging from 0=absent to 5=severe and distribution was assessed on a 6-point scale ranging from 0=none; 1=1%–10%; 2=11%–20%; 3=21%–30%; 4=31%–40%; 5=41%–50%.

FIGURE 1. Mean percentage change from baseline:
Total inflammatory lesions.



Safety assessments were made throughout the course of the study by means of adverse event sign and symptom monitoring.

RESULTS**Study Disposition and Baseline Characteristics**

At baseline, study demographics included 57.5% of male subjects and 42.5% female; the mean age was 21.4 ± 9.9 years. Of the study subjects, 65% were Caucasian and 35% African-American. Twenty subjects were treated with either tretinoin 0.04% microsphere gel dispensed by pump (TMG PUMP), or tazarotene 0.05% cream (TAZ).

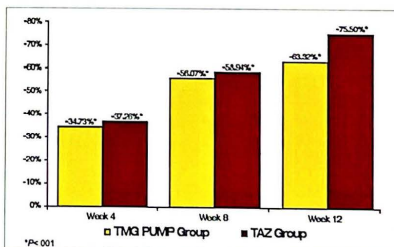
Efficacy: Investigator Global Assessment Results

At baseline, both groups had similar mean investigator global assessment (IGA) scores. By week 4, the mean IGA had decreased by -0.18 in the TMG PUMP group and by -0.05 in the TAZ group, with 29.4% of the TMG PUMP group having at least a 1 point improvement in IGA versus 20.0% in the TAZ group. However, by week 8, the changes from baseline in IGA were -0.24 in the TMG PUMP group and -0.40 in the TAZ group, with 47% of the TMG PUMP group and 45% of the TAZ group experiencing an improvement of at least 1 point from baseline. By week 12, the change from baseline in IGA was -0.73 in the TMG PUMP group and -0.95 in the TAZ group. There was no statistical significance between groups at any time point with regard to IGA.

Efficacy: Inflammatory Lesion Results

TMG PUMP produced a more rapid improvement in papule counts from baseline to week 4 than the TAZ group (mean change of -4.41 versus -3.95, respectively). This difference narrowed by week 8, with a mean papule count of 3.53 in the TMG PUMP group and 3.70 in the TAZ group. At week 12, the TMG PUMP still had a slight advantage over TAZ with regard to papule counts (3.13 versus 3.45), although these inter-group differences did not reach statistical significance.

FIGURE 2. Mean percentage change from baseline:
Total non-inflammatory lesions.



TAZ produced a more rapid change in pustule counts from baseline (mean decrease of -0.75 in the TAZ group versus -0.47 in the TMG PUMP group). At week 8, the mean decrease in pustule counts from baseline was -0.82 in the TMG PUMP group and -1.15 in the TAZ group. At week 12, the mean decrease was -1.20 in the TMG PUMP group and -1.40 in the TAZ group. Figure 1 summarizes the mean percentage changes from baseline to weeks 4, 8 and 12 for total inflammatory lesions.

Efficacy: Non-Inflammatory Lesion Results

There was a statistically significant mean percentage change from baseline in open comedone count in the TMG PUMP at -64.26% ($P=0.0039$, within group), but not the TAZ group at -19.17%. This trend continued at week 8, where the mean percentage change from baseline was -85.43% in the TMG PUMP group and -39.80% in the TAZ group. At week 12, both groups showed significant intra-group differences, with a mean percentage change of -92.65% in the TMG PUMP group ($P=0.0020$) and -79.55% in the TAZ group ($P=0.0078$).

At week 4, the mean decrease from baseline in closed comedone counts was very similar between groups (-5.47 in the TMG PUMP group) and (-6.00 in the TAZ group). At week 8, the mean decreases in closed comedones were -8.24 and -9.35, respectively. By week 12, the mean changes from baseline were -8.87 and -11.60, respectively. Figure 2 summarizes the mean percentage changes from baseline at weeks 4, 8 and 12 for all non-inflammatory lesions.

Tolerability Results: Erythema Assessments

At baseline, 25.0% of those in the TMG PUMP group and 45.0% of those in the TAZ group had moderate or severe erythema, with mean erythema scores of 1.75 and 2.05, respectively. By week 4, those in the TMG PUMP group had a slightly increased mean erythema severity score at 1.82 versus 1.75 in the TAZ group. At week 8, the mean erythema scores were 1.35 and 1.40, respectively. By week 12, 66.7% of the TMG PUMP group had shown a decrease of at least 1 or 2 points, while 95% of the TAZ group had shown these decreases. However, none of the subjects in the TMG PUMP group and 5.0% of the TAZ group had at least a 1 point increase in erythema.

Tolerability Results: Dryness Assessments

At baseline, mean dryness scores were 0.60 ± 0.88 in the TMG PUMP group and 0.40 ± 0.82 in the TAZ group. At week 4, the increase from baseline in dryness was statistically significant in the TAZ group ($P=0.0039$) as seen in Figure 3A.

At week 8, the dryness score was 0.47 ± 0.80 in the TMG PUMP group and 0.65 ± 0.93 in the TAZ group. From baseline to week 8, 52.9% of the TMG PUMP group and 20% of the TAZ group reported at least a 1 or 2 points' decrease in dryness, and 41.1% and 45%, respectively had at least 1 or 2 points' increase in

dryness. From baseline to week 12, 26.7% of the TMG PUMP group reported at least a 2 point decrease in dryness and 26.7% reported at least a 1 point decrease versus 5% and 25% of the TAZ group, respectively.

FIGURE 3A. Dryness assessments: Mean change from baseline.

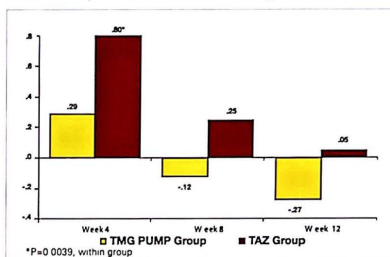


FIGURE 3B. Peeling assessments: Mean change from baseline.

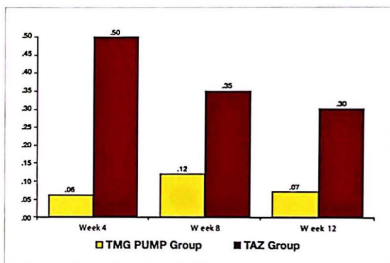
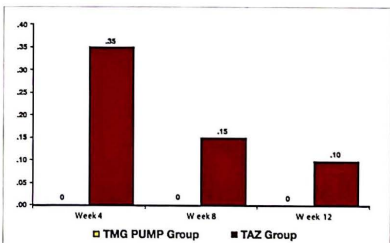


FIGURE 3C. Subject pruritus assessments: Mean change from baseline.



Tolerability Results: Peeling Assessments

Figure 3B shows the mean change (decrease or increase) from baseline to week 12, which was significant between the two groups in this study. At baseline, there was no peeling in 100% of the TAZ group and 95% of the TMG PUMP group, with 5% of the latter reporting a trace of peeling. By week 4, skin peeling was increased by 2 points in 25% of the TAZ group and 0.0% of the TMG PUMP group ($P=0.0498$), which is statistically significant between two groups.

By week 8, none of the subjects in the TAZ group and 5.9% of the subjects in the TMG PUMP group reported a decrease of at least 1 point in peeling. While 11.8% of the subjects in the TMG PUMP group and 20% of subjects in the TAZ group reported an increase of peeling by at least 1 point, and 5.9% and 15.0%, respectively, reported an increase of at least 2 points. By week 12, none of the TAZ group had shown a decrease in peeling while 6.7% of the MG group had, and 13.3% of the TMG PUMP group had a 1 point increase versus 20% of the TAZ group. None of the TMG PUMP group had an increase of at least 2 points versus 10% of the TAZ group.

Tolerability Results: Pruritus Assessments

Figure 3C shows the pruritus assessments (decrease or increase) from baseline to week 12. At baseline, 100% of the TMG PUMP group while in the TAZ group, 85% of subjects reported no pruritus and 15% of the TAZ group reported a trace. At week 4, pruritus was unchanged in the TMG PUMP group, while 25% of the TAZ group had an increase of at least 1 point ($P=0.0498$) which is also statistically significant between groups.

From baseline to week 8, there was no pruritus reported by subjects in the TMG PUMP group while 20% of the TAZ group had shown an increase of at least 1 point. At week 12, there was still no pruritus reported in the TMG PUMP group while 10% of the subjects in the TAZ group reported a decrease of at least 1 point, 10% reported an increase of at least 1 point, and 5% reported an increase of at least 2 points.

Tolerability Results: Burning Assessments

Burning scores were similar at baseline, with 95% of both groups reporting no burning. However 5% of the subjects in the TMG PUMP group reported trace level of burning, and 5% of the TAZ group reported mild burning. From baseline to week 4, there was at least a 1 point decrease in burning in 5.9% of the TMG PUMP group and 5% of the TAZ group. At least 1 point increases were seen in 23.5% in the TMG PUMP group and 25% in the TAZ group, respectively, and increases of at least 2 points were seen in 5.9% of the TMG PUMP group and 20% of the TAZ group.

From baseline to week 8, there was no decrease in burning in the TMG PUMP group, but 5% of the TAZ group had decreased by at least 1 point and 5% by at least 2 points. There had been

an increase of at least 1 point in 23.5% of the TMG PUMP group and 15% of the TAZ group, while there had been at least a 2 point increase in burning in the 5.9% of the TMG PUMP group and 5% of the TAZ group.

From baseline to week 12, 0% of the TMG PUMP group had at least a 2 point decrease and 6.7% had at least a 1 point decrease. At this time point, 10% of the TAZ group had at least a 1 point increase and 5% had at least a 2 point increase in burning from baseline.

Post-Inflammatory Hyperpigmentation (PIH) Assessments

PIH distribution was similar in both groups. Mean PIH distribution was slightly higher at baseline in the TAZ group. At week 4, 11.8% of the TMG PUMP group and 10.0% of the TAZ group had had a decrease of at least 1 point, but 0.0% of the TMG PUMP group and 5.0% of the TAZ group had an increase of at least 1 point. By study end, 53.4 of the TMG PUMP group and 50% of the TAZ group had a 1 or 2 point decrease in PIH distribution, and 5% of the TAZ group had a 1 point increase versus 0% in the TMG PUMP group.

PIH severity was slightly lower in the TAZ group at baseline (0.95 versus 1.30). By week 4, 11.8% of the TMG PUMP group and 20.0% of the TAZ group had at least a 1 point decrease in PIH severity, and 0.0% of the TMG PUMP group and 5.0% of the TAZ group had at least a 1 point increase. At week 12, 13.3% of the TMG PUMP group and 15.0% of the TAZ group had at least a 2 point decrease in PIH severity and 46.7% and 50.0%, respectively, had at least a 1 point decrease.

Adverse Events

There were adverse events (AEs) in 55.6% of the TMG PUMP group and 45.0% of the TAZ group. In the TMG PUMP group, slightly more (0.4%) of AEs were considered related to study treatment than in the TAZ group (0.2%).

DISCUSSION

This pilot study showed comparable efficacy between tretinoin microsphere gel 0.04% dispensed by pump (TMG PUMP) and tazarotene cream 0.05% (TAZ) in the treatment of mild-to-moderate facial acne. However, despite having similar overall efficacy rates, the TMG PUMP group showed more rapid results in several study parameters. There was a substantial trend toward more rapid improvement in the mean change from baseline for both papules and open comedones in the TMG PUMP group.

At week 4, skin dryness was significantly increased in subjects within the TAZ group, by at least 1 point, while there was no significant increase in the TMG PUMP group. At week 4, it is interesting to note in this study that the 2 point increase in peeling and the 1 point increase in pruritus was more statistically significant in the TAZ group than the TMG PUMP group.

Typical retinization effects such as peeling and itching were more frequently reported in the subjects in the TAZ group in this study, which reached statistically significant differences between groups at week 4. While there seemed to be similar efficacy between the treatment groups, tolerability appeared to be greater for the TMG PUMP. In clinical practice, this may translate into improved adherence with treatment.

The selection of an acne treatment regimen should be individualized for each patient to optimize the balance between efficacy and tolerability as well as to take into account skin sensitivity and patient preferences regarding vehicle. Future, larger studies comparing topical retinoids might further clarify the relationship among cutaneous tolerability, treatment adherence and therapeutic success.

DISCLOSURE

Dr. Leon Kircik is an investigator and speaker for, and advisor to, Johnson & Johnson, Galderma Laboratories, Medicis Pharmaceuticals and Stiefel Laboratories.

REFERENCES

1. Tangheiti E, Abramovits W, Solomon B, et al. Tazarotene versus tazarotene plus clindamycin/benzoyl peroxide in the treatment of acne vulgaris: A multicenter, double-blind, randomized, parallel-group trial. *J Drugs Dermatol*. 2007;5(3):256-261.
2. Gollnick H, Schramm M. Topical drug treatment in acne. *Dermatol*. 1998;196(1):119-125.
3. Thielitz A, Helmdach M, Ropke EM, Gollnick H. Lipid analysis of follicular casts from cyanoacrylate strips as a new method for studying the therapeutic effects of antiacne agents. *Br J Dermatol*. 2001;145(1):19-27.
4. Gollnick H, Cunliffe W, Berson D, et al. Management of Acne: A report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol*. 2003;49(1 Suppl):S1-S38.
5. Millikan LE. Adapalene: An update on new comparative studies between the various retinoids. *Int J Dermatol*. 2000;39(10):784-788.
6. Chandraratna RA. Rational design of receptor-selective retinoids. *J Am Acad Dermatol*. 1998;39(4 Pt 2):S124-S128.
7. Bershad S. Developments in topical retinoid treatment for acne. *Sem Cutan Med Surg*. 2001;20(3):154-161.
8. Zaenglein AL, Thiboutot DM. Expert committee recommendations for acne management. *Pediatrics*. 2006;118(3):1188-1199.

ADDRESS FOR CORRESPONDENCE

Leon H. Kircik, MD, FAAD

Physicians Skin Care, PLLC
1169 Eastern Parkway 2310
Louisville, KY 40217

Phone:(502) 456-2783

Fax:(502) 456-2728

E-mail: wedoderm@bellsouth.net



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