Comparison of Tazarotene and Minocycline Maintenance Therapies in Acne Vulgaris

A Multicenter, Double-blind, Randomized, Parallel-Group Study

James Leyden, MD; Diane M. Thiboutot, MD; Alan R. Shalita, MD; Guy Webster, MD, PhD; Kenneth Washenik, MD, PhD; Bruce E. Strober, MD, PhD; Jerome Shupack, MD

Objective: To evaluate the efficacy of 3 maintenance regimens (topical tazarotene, oral minocycline hydrochloride, or both) in sustaining improvement in acne.

Design: Multicenter, open-label treatment phase followed by double-blind, randomized, parallel-group maintenance phase.

Setting: Ambulatory patients in research or referral centers.

Patients: Volunteer sample of 189 patients with moderately severe to severe acne vulgaris (110 entered maintenance phase, 90 completed, and 2 discontinued because of adverse events).

Interventions: All patients were treated with 0.1% tazarotene gel (each evening) and a 100-mg capsule (twice daily) of minocycline hydrochloride for up to 12 weeks. Patients with 75% or greater global improvement at week 12 were randomly assigned to 12 weeks of maintenance therapy with tazarotene gel plus placebo capsules, vehicle gel plus minocycline capsules, or tazarotene gel plus minocycline capsules.

Main Outcome Measures: Overall disease severity, global improvement, and lesion counts.

Results: All regimens were effective in sustaining improvements in acne. After 12 weeks of maintenance therapy, the mean reductions from baseline in noninflammatory and inflammatory lesion count, respectively, were 60% and 54% with tazarotene, 52% and 66% with minocycline, and 64% and 66% with tazarotene plus minocycline. At week 24, more than 80% of patients in each group had maintained a 50% or greater global improvement from baseline, and more than 50% had maintained a 75% or greater global improvement.

Conclusions: A high percentage of patients with moderately severe to severe acne can maintain improvement in their condition with topical retinoid monotherapy. Maintenance with combination tazarotene and minocycline therapy showed a trend for greater efficacy but no statistical significance vs tazarotene alone. Topical retinoid monotherapy should be considered for maintenance to help minimize antibiotic exposure.

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For many years antibiotic therapy has been the backbone of treatment for inflammatory acne. However, studies have shown that topical retinoids also offer efficacy against inflammatory acne1-3 and that the combination of a topical retinoid and an antibiotic results in faster and more complete clearing of inflammatory lesions than either drug alone.4-6

See also pages 597 and 638

The reduced sensitivity of Propionibacterium acnes to antibiotics is a growing problem; the overall incidence of such resistance increased from 20% in 1978 to 62% in 1996.7 Resistance is a major issue not only because it can result in treatment failure but also because of concerns that it may potentially be transferred to other bacteria that antiacne antibiotics are used against.8 One of the most important factors that predispose patients to the development of resistant strains of P acnes is the prolonged use of antibiotics.9 Therefore, to help minimize the development of such resistance, it is evident that maintenance strategies for acne should aim to discontinue or at least minimize the long-term use of antibiotics. It has been recommended that antibiotic therapy should be limited to 3 months.8,10 Topical retinoids are a rational choice for maintenance therapy because of their activity on microcomedos (the precursor for all other acne lesions).11 Nevertheless, data evaluating their use in a main-
tenance setting are lacking. We sought to determine whether patients with moderately severe to severe inflammatory acne who had achieved a good level of clearance (eg, ≥75%) could maintain the improvement in their acne using maintenance therapy. We evaluated the efficacy of 3 maintenance therapies (tazarotene, minocycline hydrochloride, and tazarotene plus minocycline) in sustaining the clinical improvement attained after initial tazarotene plus minocycline therapy.

METHODS

STUDY DESIGN

This multicenter study was composed of a 12-week, open-label treatment phase followed by a 12-week, double-blind, randomized, parallel-group maintenance phase. Patients were eligible to enter the double-blind phase if they showed a 75% or greater global improvement at the end of the initial open-label phase. The study was approved by the appropriate institutional review boards and conducted according to the Declaration of Helsinki principles.

INCLUSION CRITERIA

Patients were eligible for enrollment in the study if they were at least 12 years of age and had moderately severe to severe facial acne vulgaris, 10 to 100 facial noninflammatory acne lesions, 25 to 60 facial inflammatory acne lesions, and no more than 2 facial nodular cystic lesions. All patients or their guardians were required to provide signed informed consent.

EXCLUSION CRITERIA

Exclusion criteria included patients who (1) had acne vulgaris known to be resistant to oral antibiotics; (2) were pregnant, breastfeeding, or planning a pregnancy; (3) had any uncontrollable systemic disease; or (4) had been participating in another study in the preceding 30 days. In addition, the following washout periods were required: 14 days for topical acne medications, 30 days for oral antibiotics and investigational drugs, 12 weeks for estrogens or birth control pills if they had been used for less than 12 weeks, and 2 years for oral retinoids.

TREATMENT REGIMEN

During the initial 12-week, open-label treatment phase, patients were requested to apply 0.1% tazarotene gel to their face each evening and to take one 100-mg minocycline hydrochloride capsule orally, twice daily. With regard to the application of tazarotene gel, the patients were instructed to apply a pea-sized amount to the face in a thin film 15 to 20 minutes after washing with a mild nonmedicated cleanser and drying with a soft towel. Patients were supplied with a noncomedogenic moisturizer to use if facial dryness developed. No other lotions, creams, medicated powders, or solutions were allowed on the treatment area.

At week 12, global response to treatment was rated by the investigator as 100% improvement (relative to baseline), approximately 90% improvement, approximately 75% improvement, approximately 50% improvement, approximately 25% improvement, no change, or worsening. Patients who had achieved at least 75% global improvement were randomly assigned to one of the following maintenance therapies for an additional 12 weeks: 0.1% tazarotene gel each evening plus a placebo capsule twice daily, vehicle gel each evening plus a 100-mg minocycline hydrochloride capsule twice daily, or 0.1% tazarotene gel each evening plus a 100-mg minocycline capsule twice daily.

RANDOMIZATION AND BLINDING PROCEDURES

Patients who achieved at least 75% global improvement at week 12 were assigned a unique patient number obtained from a computer-generated randomization schedule (using a block size of 6) provided by the sponsor. The assignment of numbers was not necessarily continuous (because one investigator may have received noncontiguous blocks of numbers) but was always in blocks of 6. The labels on the medication containers were concealed.

MAIN OUTCOME MEASURES

The main outcome measures were overall disease severity, global response to treatment, mean percentage change in open plus closed comedo count, mean percentage change in papule plus pustule count, peeling, erythema, dryness, burning, and pruritus. Overall disease severity was rated on a 7-point scale, with 0 indicating none; 2, mild; 4, moderate; and 6, severe, with 1, 3, and 5 as intermediate grades. Global response to treatment was rated as 100% improvement, approximately 90% improvement, approximately 75% improvement, approximately 50% improvement, approximately 25% improvement, no change, or worsening. Peeling, erythema, dryness, burning, and pruritus were rated as none, trace, mild, moderate, marked, or severe.

STATISTICAL ANALYSIS

The clinical hypothesis under evaluation was that there were no significant between-group differences in the incidence of patients maintaining a 75% or greater global improvement from baseline at week 24. Between-group differences were evaluated using the following tests12: 1-way analysis of variance for the mean overall disease severity score, Fisher exact test for the incidence of a 50% or greater or a 75% or greater global improvement from baseline, 1-way analysis of variance for the mean percentage reduction from baseline in lesion count, χ² test or Fisher exact test for the percentage of patients maintaining a 70% or greater or a 90% or greater reduction in lesion count attained during the initial treatment phase, and Fisher exact test for the percentage of patients with at least a 2-grade worsening in overall disease severity (eg, from mild to moderate or from moderate to severe) between weeks 12 and 24. For 3-way comparisons across all treatment regimens, a 2-sided P<.05 was considered statistically significant. If P<.05, pairwise comparisons were performed and were considered statistically significant if P<.0167 (.05/3).

RESULTS

PATIENTS

A total of 189 ambulatory patients with moderately severe to severe inflammatory acne were enrolled from 5 investigational sites in the United States. The sites were referral or research centers, and enrollment was generally performed by investigators who recruited their existing patients or patients who responded to an advertisement. Of the 189 patients evaluated, 137 (72%) completed the initial treatment phase. Of these, 114 pa-
patients (83%) achieved a 75% or greater improvement, 110 entered the maintenance phase, and 90 completed the maintenance phase (Figure 1).

The patients’ mean age was 22 years, and they were predominantly female (55%) and either white (45%) or African American (36%). The patients’ skin was most likely to be normal to oily (33%), oily (21%), or normal (16%). Their Fitzpatrick skin type was most likely to be type IV (26%), type VI (24%), or type V (21%). More than 80% of patients had had acne for at least 3 years. Baseline lesion counts (in all patients and specifically in those randomized to maintenance therapy) are summarized in Table 1.

After patients were randomized into the 3 maintenance groups, their demographic details were comparable with no significant between-group differences. However, a much larger proportion of the patients who did not continue into the maintenance phase had Fitzpatrick skin type VI (40%) than those who continued (12%).

**Efficacy**

All 3 maintenance regimens were effective in sustaining the improvement in acne achieved during initial treatment with tazarotene plus minocycline. No statistically significant differences among the 3 maintenance regimens were detected at any point for any of the following: mean overall disease severity score (Table 2 and Figure 2), percentage of patients maintaining a 50% or greater or a 75% or greater global improvement (Table 2 and Figure 3), mean percentage change from baseline in noninflammatory or inflammatory lesion counts (Table 2 and Figure 4), or percentage of patients showing good or excellent maintenance (defined as maintaining a ≥70% or ≥90% reduction in noninflammatory or inflammatory lesion counts attained during the initial treatment phase) (Table 2). Nevertheless, even though no significant between-group differences occurred, the data suggest that efficacy against inflammatory acne was slightly greater with minocycline alone or
tazarotene plus minocycline than with tazarotene alone (at week 24, a 12% to 13% greater reduction in inflammatory lesion count and a 14% to 16% greater incidence of patients with ≥75% global improvement) (Table 2).

The maximum incidence of patients reporting a ≥75% or greater global improvement from baseline at week 24 was 70% (in the tazarotene plus minocycline group). A power calculation showed that the study had 80% power to detect a statistically significant between-group difference in this parameter only if this incidence had been at least 36% lower in the other groups. Because the greatest between-group difference reported for this parameter in the trial was actually 16% (95% confidence interval, −8% to 40%), it is evident that with a power of 80%, a larger sample size would be necessary to be able to detect a statistically significant between-group difference in this parameter (if any exists at all).

Table 1. Lesion Counts at Baseline*

<table>
<thead>
<tr>
<th>Lesion Count</th>
<th>All Patients in Study (N = 189)</th>
<th>All Patients (n = 110)</th>
<th>Tazarotene (n = 36)</th>
<th>Minocycline Hydrochloride (n = 37)</th>
<th>Tazarotene and Minocycline Hydrochloride (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninflammatory lesion count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>40 ± 24.4</td>
<td>42 ± 24.5</td>
<td>44 ± 27.2</td>
<td>39 ± 22.6</td>
<td>43 ± 24.0</td>
</tr>
<tr>
<td>Median (range)</td>
<td>34 (6-100) [n = 188]†</td>
<td>39 (6-100) [n = 107]</td>
<td>34 (12-100) [n = 35]</td>
<td>35 (10-95) [n = 37]</td>
<td>42 (6-100) [n = 35]</td>
</tr>
<tr>
<td>Inflammatory lesion count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>35 ± 11.1</td>
<td>36 ± 12.1</td>
<td>37 ± 12.6</td>
<td>35 ± 12.7</td>
<td>37 ± 11.1</td>
</tr>
<tr>
<td>Median (range)</td>
<td>31 (17-84) [n = 189]‡</td>
<td>32 (18-84) [n = 108]</td>
<td>34 (22-60) [n = 35]</td>
<td>30 (18-84) [n = 37]</td>
<td>32 (23-60) [n = 36]</td>
</tr>
<tr>
<td>Total lesion count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>75 ± 30.3</td>
<td>79 ± 31.2</td>
<td>81 ± 35.6</td>
<td>75 ± 27.6</td>
<td>80 ± 30.6</td>
</tr>
<tr>
<td>Median (range)</td>
<td>66.5 (33-160) [n = 188]</td>
<td>73 (33-160) [n = 107]</td>
<td>75 (38-152) [n = 35]</td>
<td>71 (33-145) [n = 37]</td>
<td>74 (35-160) [n = 35]</td>
</tr>
</tbody>
</table>

*Sample sizes given after the ranges indicate the number of patients for whom data were available on case report forms.
†Three patients did not meet the inclusion criterion of 10 to 100 noninflammatory lesions.
‡Twelve patients did not meet the inclusion criterion of 25 to 60 inflammatory lesions.

Table 2. Efficacy Data at the End of the Maintenance Phase*

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Tazarotene</th>
<th>Minocycline Hydrochloride</th>
<th>Tazarotene and Minocycline Hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall disease severity score, mean ± SD</td>
<td>2.7 ± 1.22</td>
<td>2.3 ± 1.32</td>
<td>2.1 ± 1.52</td>
</tr>
<tr>
<td>Incidence of ≥50% global improvement from baseline (n/N)</td>
<td>81 (21/26)</td>
<td>81 (25/31)</td>
<td>87 (26/30)</td>
</tr>
<tr>
<td>Incidence of ≥75% global improvement from baseline (n/N)</td>
<td>54 (14/26)</td>
<td>68 (21/31)</td>
<td>70 (21/30)</td>
</tr>
<tr>
<td>Percentage change in noninflammatory lesion count from baseline, mean ± SD (median)</td>
<td>−60.0 ± 22.9 (−62.0)</td>
<td>−52.0 ± 30.4 (−53.0)</td>
<td>−64.0 ± 42.1 (−74.0)</td>
</tr>
<tr>
<td>Percentage change in inflammatory lesion count from baseline, mean ± SD (median)</td>
<td>−54.0 ± 25.1 (−54.0)</td>
<td>−66.0 ± 29.4 (−73.0)</td>
<td>−66.0 ± 27.2 (−75.0)</td>
</tr>
<tr>
<td>Patients maintaining ≥70% of the reduction in noninflammatory lesion count attained in the initial treatment phase (n/N)</td>
<td>81 (22/27)</td>
<td>71 (22/31)</td>
<td>90 (27/30)</td>
</tr>
<tr>
<td>Patients maintaining ≥90% of the reduction in noninflammatory lesion count attained in the initial treatment phase (n/N)</td>
<td>63 (17/27)</td>
<td>65 (20/31)</td>
<td>70 (21/30)</td>
</tr>
<tr>
<td>Patients maintaining ≥70% of the reduction in inflammatory lesion count attained in the initial treatment phase (n/N)</td>
<td>67 (18/27)</td>
<td>84 (26/31)</td>
<td>77 (24/31)</td>
</tr>
<tr>
<td>Patients maintaining ≥90% of the reduction in inflammatory lesion count attained in the initial treatment phase (n/N)</td>
<td>33 (9/27)</td>
<td>65 (20/31)</td>
<td>55 (17/31)</td>
</tr>
</tbody>
</table>

*The between-group comparisons were nonsignificant for all variables. Significance was first assessed across all 3 regimens, and if \( P < .05 \), pairwise comparisons were performed. These were considered significant if \( P < .0167 \).

Figure 2. Overall disease severity. No significant between-group differences were seen during the maintenance phase. Reprinted with permission from Elsevier Inc from “Maximizing Results in the Treatment of Acne and Improving Facial Appearance” (Skin & Allergy News. 2005;36:8-10). Minocycline was administered as minocycline hydrochloride.
No statistically significant between-group differences were detected in the percentage of patients who showed at least a 2-grade worsening in overall disease severity (eg, from mild to moderate or from moderate to severe) during the maintenance phase. The highest percentage of patients with this degree of worsening at any time during the maintenance phase was 11% (3/28) with tazarotene monotherapy (at week 24), 13% (4/32) with minocycline monotherapy (at week 20), and 6% (2/31) with tazarotene plus minocycline (at week 24) (Figure 5). Maintenance of clinical improvement is shown in Figure 6 (for tazarotene monotherapy), Figure 7 (for minocycline monotherapy), and Figure 8 (for tazarotene plus minocycline).

**TOLERABILITY**

All regimens were well tolerated. The maximum median scores were "none" for burning and pruritus and "trace" for peeling, erythema, and dryness. In the initial treatment phase, the most common adverse events considered probably related to treatment were burning (3%; 6/189), peeling (3%; 6/189), and erythema (2%; 4/189). No adverse events occurred in the maintenance phase that were considered probably related to treatment.

**COMMENT**

In this study, we evaluated maintenance therapy after initially controlling moderately severe to severe acne using oral antibiotic plus topical retinoid therapy. The question of how best to proceed once control has been achieved has not been previously studied, and our approach was to compare each agent alone and in combination. Patients who entered the maintenance phase had a mean total lesion count of 79 at the baseline visit and a mean inflammatory lesion count of 36. In view of the severity of the inflammatory aspect of acne in this patient population, we thought that a nontreatment group would have been unethical. However, if such a group had been included, it would have been of value in evaluating the rate of relapse in the absence of further treatment.

**Figure 3.** Percentage of patients with a 50% or greater global improvement (A) and a 75% or greater global improvement (B) from baseline. No significant between-group differences were seen during the maintenance phase. Minocycline was administered as minocycline hydrochloride.

**Figure 4.** Mean percentage reduction from baseline in noninflammatory lesion count (A) and inflammatory lesion count (B). No significant between-group differences were seen during the maintenance phase. Minocycline was administered as minocycline hydrochloride.

**Figure 5.** Percentage of patients with at least a 2-grade worsening of acne between the start and end of the maintenance phase. Minocycline was administered as minocycline hydrochloride.
Figure 6. Improvement in acne with tazarotene plus minocycline hydrochloride therapy for 12 weeks and maintenance of improvement with tazarotene monotherapy maintenance therapy (from week 12 to week 24). Photographs courtesy of Drs Leyden and Thiboutot. The photographs in section A are reprinted with permission from Elsevier Inc from "Maximizing Results in the Treatment of Acne and Improving Facial Appearance" (Skin & Allergy News. 2005;36:8-10).

Figure 7. Improvement in acne with tazarotene plus minocycline hydrochloride therapy for 12 weeks and maintenance of improvement with minocycline monotherapy maintenance therapy (from week 12 to week 24). Photographs courtesy of Drs Leyden and Thiboutot.
The initial treatment with minocycline and topical tazarotene (during the open-label phase) resulted in 75% or greater improvement from baseline in 60% of patients. All 3 maintenance regimens were associated with sustained reductions in both noninflammatory and inflammatory lesions during the subsequent 12-week maintenance phase. At the end of the maintenance phase, the mean reduction from baseline in the noninflammatory lesion count was 60% with tazarotene, 52% with minocycline, and 64% with tazarotene plus minocycline. Similarly, the mean reduction from baseline in the inflammatory lesion count was 54% with tazarotene, 66% with minocycline, and 66% with tazarotene plus minocycline. At the end of the maintenance phase, more than 80% of patients in each treatment group had maintained a 50% or greater global improvement from baseline, and more than 50% had maintained a 75% or greater global improvement. Although no statistically significant differences were found between the maintenance regimens, there was a trend for combination minocycline and tazarotene therapy to be more effective in sustaining the improvements in acne than tazarotene alone. There was also a trend for minocycline alone to show greater maintenance of improvement than tazarotene alone for inflammatory lesions but not for noninflammatory lesions. With an increased sample size, it is possible that these trends might reach statistical significance.

Using lesion counts and global improvement to evaluate the maintenance of efficacy has limitations. First, the percentage reduction from baseline in lesion count at the end of maintenance therapy may be influenced by the degree of clinical improvement achieved during initial treatment and not solely the efficacy of maintenance therapy. Second, global improvement does not differentiate between noninflammatory and inflammatory acne and may be reliant on the investigator’s memory if baseline photography is not available for comparison. Furthermore, because inflammatory acne is so much more visually apparent than noninflammatory acne, global improvement may be biased toward improvements in inflammatory acne.

Maintenance is a difficult concept to define, and because the efficacy of maintenance therapy has not been discussed extensively in the literature, no consensus exists regarding what level of maintenance is considered to be useful clinically and during what period. Although it is likely that physicians and patients may have differing perspectives on this, it would be valuable if future research in this area could adopt standard definitions to facilitate objective comparisons. Ideally, we need to determine the degree to which the clinical improvement in noninflammatory and inflammatory acne attained during initial treatment is preserved during maintenance therapy. In this article we present our method of evaluating this: the incidence of patients who, after 12 weeks of maintenance therapy, had maintained a 70% or greater or a 90% or greater reduction in lesion counts attained during the initial treatment phase. These values serve as indicators of what might be considered good or excellent maintenance, respectively.

An alternative means of communicating the efficacy of maintenance is to present the percentage of patients who show a clinically relevant worsening in overall disease severity. In this study, at any point during the maintenance phase, no more than 13% of patients in any group showed a worsening in the severity of their acne of at least 2 grades. Although this statement has clinical relevance that is easy for both physicians and patients to understand, it may not be useful for research purposes, since...
it does not allow us to differentiate between noninflammatory and inflammatory acne, it may not be sensitive enough to detect relatively small differences between regimens, and it is focused not on what we are trying to achieve as physicians (maintenance) but on failure.

In this study, maintenance treatment was well tolerated with no adverse events that were considered probably related to treatment. These data attest to the good tolerability of the treatment regimens and also indicate that blinding during the maintenance phase was likely not compromised by any potential differences in tolerability among the treatment regimens.

This study involved only patients with moderately severe to severe acne, and in future studies, it would be useful to evaluate the benefit of topical retinoids as maintenance therapy in a greater number of individuals and in patients with less severe acne. It would also be interesting to explore whether the degree to which improvement in acne is maintained could be enhanced further by the addition of other nonantibiotic therapies such as benzoyl peroxide. This could help ensure maximum long-term efficacy while sparing the use of antibiotics. Nevertheless, even without such potential adjunctive therapy, some patients who respond well to initial treatment with tazarotene plus minocycline can maintain improvement in their acne with tazarotene monotherapy.

CONCLUSIONS

Initial treatment with tazarotene plus minocycline is effective in improving moderately severe to severe acne. Furthermore, the improvements can be well maintained even with the topical retinoid as a single agent. Monotherapy with the topical retinoid has clinical advantages for ongoing maintenance therapy compared with the topical retinoid plus minocycline or minocycline alone; obviating the need for long-term treatment with oral antibiotics helps prevent potential problems such as the development of P. acne resistance.

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Correspondence: James Leyden, MD, Skin Study Center, 505 Parkway, First Floor, Broomall, PA 19008 (jgleiden@mindspring.com).

Author Contributions: Study concept and design: Leyden, Shalita, Webster, and Washenik. Acquisition of data: Leyden, Thiboutot, Shalita, Webster, Washenik, Strober, and Shupack. Analysis and interpretation of data: Leyden, Webster, and Strober. Drafting of the manuscript: Webster. Critical revision of the manuscript for important intellectual content: Leyden, Thiboutot, Shalita, Webster, Washenik, Strober, and Shupack. Obtained funding: Leyden. Administrative, technical, and material support: Leyden, Webster, Washenik, Strober, and Shupack. Study supervision: Thiboutot, Shalita, Webster, Washenik, and Strober. This study was conducted and the data were collected by the investigators in collaboration with an independent clinical research organization. Management and analysis of the data were performed by the clinical research organization. Interpretation of the data was the result of collaboration among the independent medical writer, the investigators, and Allergan Inc. All authors were study investigators.

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REFERENCES