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Original Research Article

COMPARISON OF EFFICACY OF TOPICAL MINOCYCLINE WITH TOPICAL TRIFAROTENE FOR THE TREATMENT OF MODERATE TO SEVERE ACNE

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ABSTRACT

Background: Acne vulgaris is a chronic inflammatory disorder that requires effective topical therapy. Direct comparative data on topical retinoids and topical antibiotics for moderate-to-severe acne remain limited. Aim: To compare the efficacy and safety of topical trifarotene 0.005% and topical minocycline 4% in patients with moderate-to-severe acne vulgaris.

Materials and Methods: This prospective comparative study included 50 patients with moderate-to-severe acne treated at a tertiary care dermatology centre over 12 weeks. Patients received either topical trifarotene 0.005% gel (n = 25) or topical minocycline 4% gel (n = 25). Inflammatory and non-inflammatory lesion counts, Investigator's Global Assessment (IGA) scores, and adverse effects were evaluated at baseline and at 4, 8, 12 weeks.

Results: Baseline inflammatory lesion counts were comparable between the trifarotene (30.96 ± 13.11) and minocycline (36.20 ± 11.39) groups ($p = 0.138$), as were the non-inflammatory lesion counts (40.44 ± 11.92 vs. 41.92 ± 6.51; $p = 0.588$). At week 12, trifarotene produced a greater reduction in inflammatory lesions (−20.6 vs. −12.6; $p < 0.0001$) and non-inflammatory lesions (−26.76 vs. −14.44; $p < 0.0001$) than minocycline. IGA grade 0–1 was achieved in 76% of patients in the trifarotene group versus 20% in the minocycline group ($p = 0.002$). Local adverse effects were similar between the groups, whereas hyperpigmentation was significantly less frequent with trifarotene ($p = 0.038$).

Conclusion: Topical trifarotene showed superior short-term efficacy in reducing both inflammatory and non-inflammatory acne lesions compared with topical minocycline, with comparable tolerability and less hyperpigmentation.

Keywords: Acne Vulgaris; Minocycline; Retinoids; Administration, Topical; Hyperpigmentation, Skin; Trifarotene.

INTRODUCTION

Acne vulgaris is a common skin disorder characterised by the presence of inflammatory and non-inflammatory lesions.[1] It affects adolescents and young adults worldwide. The prevalence of acne among adolescents ranges from 35% to almost 100% in different countries.[2,3] Acne is mediated through a complex interaction of androgen-induced sebaceous gland stimulation, microbial dysbiosis, and innate and adaptive immunoreactivity.[4] These mechanisms contribute to the development and persistence of lesions. Acne manifests clinically as comedones, papules, pustules, and nodules on the face, neck, and trunk.[5] The disease has a chronic course in many patients. The psychological effects of acne are well documented and include reduced self-esteem, anxiety, depression, and negative social perception.6 These effects often persist after clinical improvement.

Over the years, a combination of topical and systemic agents has been used for the treatment of moderate to severe acne.[7] These include oral and topical retinoids, antibiotics, hormonal agents, and other adjunctive therapies. However, topical therapy is preferred as a first-line treatment in many patients because of better tolerability and avoidance of systemic adverse effects. Systemic and topical retinoids and antibiotics are the most commonly used drugs, either as monotherapies or in combination. Topical agents have better safety profiles and are free

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from systemic toxicity. They are suitable for long-term use in most patients.

Retinoids are synthetic derivatives of vitamin A that target follicular hyperproliferation and abnormal desquamation.[8] They normalise keratinocyte differentiation and prevent microcomedone formation. Retinoids bind to intranuclear retinoic acid or retinoid X receptors. Topical retinoids are the mainstay of treatment for acne vulgaris and are used alone or in combination with antibiotics. Trifarotene is an FDA-approved topical retinoid that binds selectively to the retinoic acid receptor gamma. This receptor is predominantly expressed in the skin. Trifarotene has shown good efficacy with improved tolerability when compared to earlier-generation retinoids.[9]

Oral and topical antibiotics reduce Cutibacterium acnes proliferation and inflammation. Minocycline is a semisynthetic, second-generation tetracycline with anti-inflammatory and bacteriostatic properties. It inhibits bacterial protein synthesis and modulates the inflammatory response. Topical 4% minocycline gel has been approved in India by the Drugs Controller General of India. The topical formulation aims to deliver high local drug concentration at the pilosebaceous unit while avoiding systemic adverse effects associated with oral minocycline.[10]

Topical retinoids and antibiotics are widely used for acne management. However, there are limited data directly comparing the efficacy and safety of topical minocycline and topical trifarotene in patients with moderate-to-severe acne vulgaris. A direct comparison may help guide the selection of treatment. This study aimed to evaluate and compare the efficacy and safety of topical minocycline gel 4% and topical trifarotene 0.005% in patients with moderate-to-severe acne vulgaris.

MATERIALS AND METHODS

This prospective comparative study included 50 patients and was conducted at the Department of Dermatology, Sri Lalithambigai Medical College and Hospital, Dr.MGR Educational and Research Institute over 18 months. Approval from the institutional ethics committee was obtained, and written informed consent was obtained from all patients.

Inclusion criteria

Patients aged >18 years of both sexes with moderate to severe acne vulgaris who provided consent were included.

Exclusion Criteria

Patients <18 years of age, truncal acne, pregnant or lactating women, those not willing to participate, and patients already receiving topical or systemic treatment for acne were excluded from the study.

Methods

At baseline, a detailed history was obtained, and a complete clinical examination was performed, including acne grading and lesion counts. The patients were divided into two groups of 25 each. Group A was treated with topical minocycline 4% gel applied once daily, whereas Group B received topical trifarotene 0.005% (Aklief cream) once daily. All patients were instructed on the correct drug application and basic skin care practices. Follow-up visits were scheduled at 4, 8, and 12 weeks. During each visit, inflammatory and non-inflammatory lesion counts were noted, acne grade and Investigator's Global Assessment score were assessed, and local side effects such as erythema, dryness, peeling, and hyperpigmentation were documented.

Statistical Analysis

Data analysis was performed using IBM SPSS v21. Data are presented as mean, standard deviation, frequency, and percentage. Continuous variables were compared using the independent sample t-test or repeated-measures analysis of variance, as appropriate. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test. Within-group comparisons of ordinal variables over time were performed using the Friedman test, with post-hoc pairwise comparisons using the Wilcoxon signed-rank test. Significance was defined as $p<0.05$ using a two-tailed test.

RESULTS

In the minocycline group, the highest number of patients were in the 21–25-year age group, with 11 patients (44%), whereas in the trifarotene group, most patients were aged 18–20 years, accounting for nine patients (36%). Females were the predominant sex in both groups, with 17 patients (68%) in each group. Regarding disease duration, acne lasting 1.1–5 years was most frequently observed in both groups, seen in 13 patients (52%) receiving minocycline and 16 patients (64%) receiving trifarotene. [Table 1]

Table 1: Baseline demographic and disease duration profile

Variable	Category	Minocycline (n = 25)	Trifarotene (n = 25)	p value
Age group (years)	18–20	4 (16%)	9 (36%)	0.157
	21–25	11 (44%)	6 (24%)	
	26–30	7 (28%)	4 (16%)	
	31–35	3 (12%)	6 (24%)	
Sex	Female	17 (68%)	17 (68%)	1
	Male	8 (32%)	8 (32%)	
Duration of acne (years)	< 1	9 (36%)	8 (32%)	0.504
	1.1–5	13 (52%)	16 (64%)	
	> 5	3 (12%)	1 (4%)	

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At baseline, inflammatory lesion counts were comparable between the minocycline (36.20 ± 11.39) and trifarotene (30.96 ± 13.11) groups (p = 0.138). From week 4 onwards, the trifarotene group showed lower inflammatory lesion counts than the minocycline group, with mean values of 23.72 ± 10.31 vs. 31.72 ± 10.11 at week 4 (p = 0.008), 16.60 ± 7.43 vs. 27.08 ± 8.73 at week 8 (p < 0.0001), and 10.36 ± 4.71 vs. 23.60 ± 7.49 at week 12 (p < 0.0001). The non-inflammatory lesion counts were similar at baseline between the minocycline (41.92 ± 6.51) and trifarotene groups (40.44 ± 11.92) (p = 0.588). On follow-up, non-inflammatory lesions were consistently lower in the trifarotene group, with mean counts of 31.16 ± 9.42 compared with 36.76 ± 5.72 at week 4 (p = 0.014), 21.96 ± 6.77 vs. 31.64 ± 5.02 at week 8 (p < 0.0001), and 13.68 ± 4.39 vs. 27.48 ± 4.32 at week 12 (p < 0.0001), indicating a greater reduction in both lesion types with trifarotene. [Table 2]

Table 2: Comparison of inflammatory and non-inflammatory lesion counts at follow-up

Lesion type	Time point	Minocycline	Trifarotene	p value
Inflammatory lesions	Week 0	36.20 ± 11.39	30.96 ± 13.11	0.138
	Week 4	31.72 ± 10.11	23.72 ± 10.31	0.008
	Week 8	27.08 ± 8.73	16.60 ± 7.43	<0.0001
	Week 12	23.60 ± 7.49	10.36 ± 4.71	<0.0001
Non-inflammatory lesions	Week 0	41.92 ± 6.51	40.44 ± 11.92	0.588
	Week 4	36.76 ± 5.72	31.16 ± 9.42	0.014
	Week 8	31.64 ± 5.02	21.96 ± 6.77	<0.0001
	Week 12	27.48 ± 4.32	13.68 ± 4.39	<0.0001

At baseline, most patients in both groups had grade 3–4 acne (Figure1), with 22 patients (88%) in the minocycline group and 17 patients (68%) in the trifarotene group, with no significant difference between groups (p = 0.371). By week 8, complete clearance (grade 0) was observed only in the trifarotene group, affecting four patients (16%) versus none in the minocycline group (p = 0.06). At week 12, a difference was evident, with 19 patients (76%) in the trifarotene group achieving grade 0 or grade 1 vs. 5 patients (20%) in the minocycline group (Figure 2), showing a significant between-group difference (p = 0.002). [Table 3]

Table 3: Comparison of acne grade (IGA score) at follow-up

Time point	Acne grade / IGA score	Minocycline	Trifarotene	p value
Week 0	Grade 2	2 (8%)	5 (20%)	0.371
	Grade 3	10 (40%)	9 (36%)	
	Grade 4	12 (48%)	8 (32%)	
	Grade 5	1 (4%)	3 (12%)	
Week 4	Grade 1	1 (4%)	5 (20%)	0.102
	Grade 2	4 (16%)	9 (36%)	
	Grade 3	14 (56%)	8 (32%)	
	Grade 4	5 (20%)	3 (12%)	
	Grade 5	1 (4%)	0	
Week 8	Grade 0	0	4 (16%)	0.06
	Grade 1	2 (8%)	4 (16%)	
	Grade 2	10 (40%)	11 (44%)	
	Grade 3	12 (48%)	4 (16%)	
	Grade 4	1 (4%)	2 (8%)	
Week 12	Grade 0	1 (4%)	8 (32%)	0.002
	Grade 1	4 (16%)	11 (44%)	
	Grade 2	14 (56%)	4 (16%)	
	Grade 3	5 (20%)	2 (8%)	
	Grade 4	1 (4%)	0	

From baseline to week 12, the mean reduction was 20.6 lesions with trifarotene versus 12.6 lesions with minocycline (p < 0.0001). Early improvement was also greater with trifarotene than with minocycline from baseline to week 4, with a reduction of 7.24 lesions versus 4.48 lesions (p < 0.0001). Continued reduction was observed between weeks 4 and 8, with 7.12 lesions with trifarotene vs. 4.64 lesions with minocycline (p < 0.0001). [Table 4]

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Table 4: Comparison of within-group reduction in inflammatory lesion counts at follow-up

Comparison period	Minocycline Mean difference (Inflammatory)	p value	Trifarotene Mean difference (Inflammatory)	p value
Baseline vs Week 4	4.48	<0.0001	7.24	<0.0001
Baseline vs Week 8	9.12	<0.0001	14.36	<0.0001
Baseline vs Week 12	12.6	<0.0001	20.6	<0.0001
Week 4 vs Week 8	4.64	<0.0001	7.12	<0.0001
Week 4 vs Week 12	8.12	<0.0001	13.36	<0.0001
Week 8 vs Week 12	3.48	<0.0001	6.24	<0.0001

From baseline to week 12, a higher reduction in non-inflammatory lesions was observed in the trifarotene group, with a mean decrease of 26.76 lesions compared with a reduction of 14.44 lesions in the minocycline group ($p < 0.0001$). An early response was evident by week 4, with trifarotene showing a reduction of 9.28 lesions versus 5.16 lesions with minocycline ($p < 0.0001$). The difference between groups persisted during follow-up, with reductions of 9.2 vs. 5.12 lesions between weeks 4 and 8 ($p < 0.0001$) and 8.28 vs. 4.16 lesions between weeks 8 and 12 ($p < 0.0001$). [Table 5]

Table 5: Comparison of within-group reduction in non-inflammatory lesion counts over follow-up

Comparison period	Minocycline Mean difference (non-inflammatory)	p value	Trifarotene Mean difference (non-inflammatory)	p value
Baseline vs Week 4	5.16	<0.0001	9.28	<0.0001
Baseline vs Week 8	10.28	<0.0001	18.48	<0.0001
Baseline vs Week 12	14.44	<0.0001	26.76	<0.0001
Week 4 vs Week 8	5.12	<0.0001	9.2	<0.0001
Week 4 vs Week 12	9.28	<0.0001	17.48	<0.0001
Week 8 vs Week 12	4.16	<0.0001	8.28	<0.0001

At week 4, the absence of erythema was more common in the trifarotene group (18 patients [72%]) than in the minocycline group (13 patients [52%]) ($p = 0.235$). At week 8, erythema was absent in 16 patients (64%) treated with minocycline vs. 9 patients (36%) treated with trifarotene ($p = 0.089$). By week 12, hyperpigmentation was higher in the minocycline group, with only seven patients (28%) showing no pigmentation changes versus 17 patients (68%) in the trifarotene group; the difference was statistically significant ($p = 0.038$). At week 4 trifarotene group (16%) showed a significant severe skin dryness and peeling compared to minocycline group (8%) but there were no significant difference at follow up visits at week 8 and 12 ($p > 0.05$). [Table 6-8]

Table 6: Group-wise comparison of adverse effect profile at 4 weeks

Adverse effect	Group	None	Mild	Moderate	Severe	p value
Erythema	Minocycline	13 (52%)	8 (32%)	4 (16%)	0	**0.235**
	Trifarotene	18 (72%)	6 (24%)	1 (4%)	0	
Skin peeling	Minocycline	14 (56%)	8 (32%)	1 (4%)	2 (8%)	**0.038**
	Trifarotene	8 (32%)	5 (20%)	8 (32%)	4 (16%)	
Hyperpigmentation	Minocycline	20 (80%)	4 (16%)	0	1 (4%)	**0.545**
	Trifarotene	19 (76%)	5 (20%)	1 (4%)	0	
Dryness	Minocycline	14 (56%)	9 (36%)	2 (8%)	0	**0.021**
	Trifarotene	5 (20%)	10 (40%)	9 (36%)	1 (4%)	

Table 7: Group-wise comparison of adverse effect profile at 8 weeks

Adverse effect	Group	None	Mild	Moderate	Severe	p value
Erythema	Minocycline	16 (64%)	5 (20%)	4 (16%)	0	**0.089**
	Trifarotene	9 (36%)	12 (48%)	4 (16%)	0	
Skin peeling	Minocycline	13 (52%)	8 (32%)	4 (16%)	0	**0.706**
	Trifarotene	13 (52%)	6 (24%)	5 (20%)	1 (4%)	
Hyperpigmentation	Minocycline	18 (72%)	3 (12%)	3 (12%)	1 (4%)	**0.624**
	Trifarotene	16 (64%)	5 (20%)	4 (16%)	0	
Dryness	Minocycline	8 (32%)	10 (40%)	5 (20%)	2 (8%)	**0.126**
	Trifarotene	3 (12%)	7 (28%)	11 (44%)	4 (16%)	

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Table 8: Group-wise comparison of adverse effect profile at 12 weeks

Adverse effect	Group	None	Mild	Moderate	Severe	p value
Erythema	Minocycline	13 (52%)	8 (32%)	4 (16%)	0	**0.466**
	Trifarotene	9 (36%)	12 (48%)	4 (16%)	0	
Skin peeling	Minocycline	13 (52%)	8 (32%)	3 (12%)	1 (4%)	**0.888**
	Trifarotene	14 (56%)	7 (28%)	2 (8%)	2 (8%)	
Hyperpigmentation	Minocycline	7 (28%)	10 (40%)	7 (28%)	1 (4%)	**0.038**
	Trifarotene	17 (68%)	5 (20%)	3 (12%)	0	
Dryness	Minocycline	12 (48%)	11 (44%)	2 (8%)	0	**0.173**
	Trifarotene	13 (52%)	6 (24%)	6 (24%)	0	

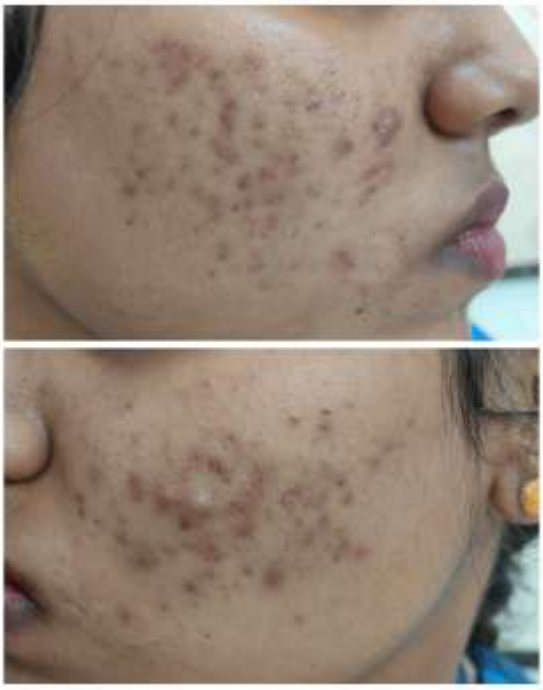

Figure 1: Grade 3 acne before treatment

Figure 2: After treatment with Trifarotene at week 8

DISCUSSION

This study showed that the baseline characteristics were comparable across the groups. Topical Trifarotene 0.005% cream produced more and earlier reductions in inflammatory and non-inflammatory lesions than topical 4% minocycline gel. Clinical improvement has increased over time. Safety was acceptable, with similar local tolerability and a lower risk of hyperpigmentation than minocycline.

In our study, the two treatment groups were comparable at baseline with respect to age, sex distribution, and acne duration, with no significant differences. Similarly, Brumfiel et al. found that the baseline groups were comparable: mean age 19.4 ± 6.4 years; males 47.9%, females 52.1%. Facial inflammatory lesions were 34.7 ± 13.0 vs. 34.8 ± 13.6, and non-inflammatory lesions were 54.0 ± 28.6 vs. 52.8 ± 26.1, with no significant differences.[11] This study finding confirms that both treatment groups started from similar baseline characteristics, as in our study. This similarity supports a fair comparison and indicates that outcome differences are likely due to treatment effects rather than baseline bias.

Our study showed that baseline lesion counts were similar; however, trifarotene achieved better inflammatory and non-inflammatory reductions than minocycline from week 4 onwards. Similarly, Tan et al. reported that baseline inflammatory lesion counts were similar between groups (34.7 ± 13.0 vs. 34.8 ± 13.6; 36.1 ± 12.5 vs. 37.1 ± 15.1). From week 4 onwards, trifarotene showed significantly better reductions, reaching −19.0 vs. −15.4 and −24.2 vs. −18.7 by week 12 ($p < 0.001$).12 Raoof et al. showed that baseline inflammatory lesion counts were similar in patients treated with FMX101 (topical minocycline 4% foam) and those receiving foam vehicle (30.7 vs. 30.8). From week 3 onwards, FMX101 produced better reductions, with a larger decrease evident by week 12 (−16.93 vs −13.40; $p < 0.0001$).[13]

Similarly, Tan et al. showed that baseline non-inflammatory lesion counts were similar (54.0 ± 28.6 vs. 52.8 ± 26.1; 50.6 ± 25.9 vs. 51.2 ± 25.8). From week 4 onwards, trifarotene achieved better reductions, reaching −25.0 vs. −17.9 and −30.1 vs. −21.6 by week 12 ($p < 0.001$).12 Kircik et al. found that baseline non-inflammatory lesion counts were comparable across studies: in FMX101 trials, mean counts were 49.7 in the topical minocycline 4% foam group and 49.6 in the vehicle group; in the trifarotene

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PERFECT trials, baseline facial non-inflammatory lesions were 53.4 ± 27.35 (PERFECT 1) and 50.9 ± 25.83 (PERFECT 2).[14] This difference is biologically plausible because topical retinoids suppress microcomedone formation and follicular hyperkeratinization, which are upstream drivers of both inflammatory and non-inflammatory acne lesions, whereas antibiotics primarily suppress Cutibacterium acnes–mediated inflammation without preventing new lesion formation.

Our study showed that baseline acne severity was similar between the groups; however, by week 12, more patients achieved a clear or almost clear status with trifarotene. Similarly, Raoof et al. found that at baseline, acne severity was comparable, with most patients classified as Investigator's Global Assessment (IGA) grade 3 or 4 (FMX101:84.0% moderate, 16.0% severe; trifarotene trials predominantly grade 3). By week 12, a higher proportion of patients achieved IGA Grade 0/1 with trifarotene (29.4–42.3%) than with topical minocycline FMX101 (30.8%).[13] Del Rosso et al. reported comparable baseline acne severity, with most subjects graded IGA 3–4. At week 12, IGA success (Grade 0/1) was higher with trifarotene + doxycycline (31.7%) than with vehicle + placebo (15.8%; $p < 0.05$), with ≥2-grade improvement in 78.3% vs 50.1%.[15] These studies show similar baselines and higher improvement with trifarotene, supporting that our findings reflect true treatment effects rather than baseline differences.

In this study, trifarotene showed greater improvement in non-inflammatory lesions with similar local tolerability, whereas hyperpigmentation was more common with minocycline. Even though Trifarotene showed increase in dryness and skin peeling in the first four weeks the tolerability improved with continuous application with no significant worsening in the trifarotene group. Likewise, Brumfiel et al. showed that in the Phase III PERFECT trials, baseline facial non-inflammatory lesion counts were comparable between groups: in PERFECT-1, trifarotene 54.0 ± 28.55 versus vehicle 52.8 ± 26.08 lesions, and in PERFECT-2, trifarotene 50.6 ± 25.93 versus vehicle 51.2 ± 25.75 lesions.[11] Alexis et al. showed that local tolerability was similar between trifarotene and the vehicle/minocycline comparator, with no significant differences in erythema, peeling, or dryness. Hyperpigmentation outcomes favoured trifarotene, showing better PAHPI reduction (−18.9% vs −11.3% at Week 24; $p < 0.01$).[16]

Similarly, Shute et al. found that minocycline is associated with cutaneous hyperpigmentation in 3–15% of patients, particularly with prolonged use, whereas trifarotene is not associated with drug-induced pigmentation. Local adverse effects, such as erythema, peeling, and dryness, are generally comparable between treatments at week 12.[17] These studies confirm comparable baselines, similar tolerability, and lower hyperpigmentation with trifarotene, supporting that its benefits reflect true efficacy and safety advantages.

Trifarotene demonstrated superior efficacy in reducing both inflammatory and non-inflammatory lesions, with an acceptable safety profile during the study period. Similarly, Blume-Peytavi et al. found that trifarotene showed sustained efficacy, with IGA success increasing from 26.6% at week 12 to 65.1% at week 52, alongside continued reductions in inflammatory and non-inflammatory lesions and an acceptable safety profile.[18] Tan et al. found that across both phase III trials, trifarotene consistently reduced inflammatory and non-inflammatory lesions more than the vehicle, while remaining well-tolerated. Most adverse effects were mild, localised, and decreased with continued use over time.[12] These studies support our findings, confirming that trifarotene provides sustained lesion reduction with good tolerability, thereby strengthening its efficacy and safety.

Strengths

The strengths of this study include its prospective design, direct head-to-head comparison of two active topical agents, repeated quantitative lesion counts, and use of the Investigator's Global Assessment for disease severity.

Limitations

The study had a short follow-up period, which limited the assessment of long-term outcomes. Being single-centred reduces generalisability. Lack of blinding may introduce bias, and microbiological or resistance outcomes were not evaluated despite using an antibiotic-based treatment. The absence of randomisation and formal sample size calculation may increase the risk of selection bias and limit the statistical power.

CONCLUSION

Topical trifarotene produced significantly better and faster reductions in both inflammatory and non-inflammatory acne lesions than topical minocycline, with comparable local tolerability and less hyperpigmentation. As a direct head-to-head comparison of two active topical agents, this study provides evidence that trifarotene provides superior short-term clinical efficacy in moderate-to-severe acne. Larger randomised trials with longer follow-ups are required to confirm these findings and evaluate long-term outcomes.

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