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Original Research Article

Evaluation of the effectiveness of the combination of doxycycline and trifarotene for managing acne vulgaris of moderate to severe severity: a study in a tertiary care hospital

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ABSTRACT

Background: Acne vulgaris (AV), affecting diverse skin types, prompts a uniform therapeutic approach, with options ranging from topical to systemic treatments. Trifarotene, a fourth-generation topical retinoid, offers precise skin-specific effects, especially in facial and truncal acne treatment. The study aimed to evaluate the effectiveness of the combination of doxycycline and trifarotene for managing AV of moderate to severe severity.
Methods: At Mymensingh medical college hospital, the study enrolled 100 individuals to evaluate a new treatment for moderate AV from Jan-Jun 2023. Treatment comprised oral doxycycline (100 mg) and topical trifarotene (0.005% w/w) over 2 months, following a stratified randomization process. Evaluation criteria included clinical scores, lesion counts, and safety parameters, analyzed using SPSS v20.
Results: Study on doxycycline and trifarotene for moderate to severe acne shows promising results. Participants, mainly aged 15-25 exhibit diverse demographics and balanced gender ratio. Significant improvement on investigator's global assessment (IGA) scale is noted, with 35% experiencing notable progress at 9-10 weeks, alongside reduction in *Propionibacterium acnes* growth and positive patient feedback with 36% reporting 'good' response.
Conclusions: The study on doxycycline and trifarotene for moderate acne exhibits robust methodology with adherence to established practices and stratified randomization. Results, assessed via IGA, demonstrate promising efficacy and safety, providing insights for diverse skin types' acne management enhancement.

Keywords: AV, Oral antibiotics, Doxycycline, Trifarotene

INTRODUCTION

Acne vulgaris (AV) is a prevalent skin condition affecting individuals across diverse skin types and racial/ethnic backgrounds. The observable manifestation of AV and the patterns of clinical response to therapeutic interventions may exhibit variations in individuals with skin of color (SoC) when compared to those with lighter skin types.[1] Due to the perceived similarity in pathophysiology and clinical presentations of facial and truncal acne, clinicians frequently employ a uniform therapeutic approach for both facial and non-facial lesions, even in the absence of conclusive evidence for truncal AV.[2-4] Severe acne can have a significant negative impact on the quality of life of patients.[5] To address severe acne, oral antibiotics are commonly prescribed in accordance with acne treatment guidelines. It is advised to exercise caution and limit the duration of treatment to the minimum required to mitigate the risk of antibiotic resistance.[6,7] Doxycycline proves beneficial in acne

treatment owing to its antibacterial and anti-inflammatory properties. The recommended regimen involves taking one capsule daily (100 mg Doxycycline) for a duration of 3 months. Prolonged antibiotic use in acne may lead to undesired side effects in patients.[8,9] In cases of facial or truncal disease where the clinician deems that topical monotherapy may not suffice, a topical retinoid might be employed in conjunction with other treatments, including an oral antibiotic.[10,11] Trifarotene, a novel fourth-generation topical retinoid, stands as a pioneering addition uniquely investigated for the treatment of both facial and truncal acne. By selectively agonizing the retinoic acid receptor (RAR)-gamma, the predominant RAR isotype in the epidermis, trifarotene delivers more precise, skin-specific effects compared to retinoids from earlier generations.[12,13]

Objective

The study aimed to evaluate clinical responses and potential side effects while adhering to established practices, employing an open-label, single-arm design with a study population of 100 individuals, to assess the efficacy and safety of a novel therapeutic regimen comprising doxycycline and trifarotene for moderate facial and truncal AV over two months.

METHODS

An observational study was conducted at the department of dermatology, mymensingh medical college hospital in Bangladesh, spanning from January 1, 2023, to June 30, 2023. The study encompassed a study population of 100 individuals. The randomization process was stratified based on study center using an interactive response technology system. The clinical trial adhered to established and widely recognized practices, as outlined in the Supplemental Information.

We assessed a novel therapeutic regimen involving the administration of doxycycline 100 mg (oral) once daily during dinner with food and water for 18 days per month, over two consecutive months. Simultaneously, participants applied topical trifarotene 0.005% w/w once daily at night following thorough cleansing, maintaining this routine for the same duration.

A wash-out period was implemented for topical treatments and any prior retinoid treatments, with a minimum duration of 2 weeks. For systemic corticosteroids, antibiotics, and spironolactone, the wash-out period was set at a minimum of 4 weeks. In the case of oral retinoids/isotretinoin, a wash-out period of 10 weeks was observed before the commencement of the study.

Study constituted open-label, single-arm investigation aimed at assessing the treatment efficacy for moderate facial and truncal AV. Participants with a baseline IGA score of 3 and a minimum of 20 inflammatory lesions and 25 noninflammatory lesions on the face, as well as 20 to 100 inflammatory lesions and 20 noninflammatory lesions on the trunk were enrolled. Trifarotene 0.005% cream was applied once daily in the evening for a duration of 12 weeks. The study documented any prior AV treatments within the preceding 6 months, and a washout period of at least 2 weeks (extended to 4 weeks for previous retinoid treatments) was observed for topical treatments on the face and trunk before the initiation of the study. The efficacy, safety, and vital signs were summarized based on analysis visits. The data underwent verification, entry, and analysis through the utilization of the SPSS version 20.

Inclusion criteria

Inclusion criteria for the study required participants to have moderate facial and truncal AV, as assessed by baseline IGA score of 3, with specific lesion counts on the face and trunk. The study enrolled individuals aged 18-40 with a minimum of 20 inflammatory lesions and 25 noninflammatory lesions on the face, as well as 20 to 100 inflammatory lesions and 20 noninflammatory lesions on the trunk.

Exclusion criteria

Exclusion criteria for the study included individuals with severe facial or truncal AV, as well as those with a history of hypersensitivity to doxycycline or trifarotene. Patients with a current or recent history of systemic retinoid use, pregnancy, lactation, or any significant medical condition affecting AV were also excluded from the study.

RESULTS

Table 1 provides an overview of the demographic characteristics and disease duration within the studied population for the investigation focusing on the effectiveness of the combination of doxycycline and trifarotene in managing moderate to severe AV.

The age distribution reveals that a significant portion of participants falls within the 15-25 age range, with 38% aged 15-20 and 41% aged 21-25. Regarding gender, the study comprises 53% male and 47% female participants. The racial breakdown shows 39% White, 31% black, and 30% from other racial backgrounds.

Table 2 illustrates the data showcases the observed improvement on the IGA scale at various treatment weeks. Notably, 5.00% of participants experienced improvement during the initial 1-2 weeks, with a consistent increase in improvement percentages observed at subsequent intervals: 13.00% at 3-4 weeks, 19.00% at 5-6 weeks, 28.00% at 7-8 weeks, and a significant 35.00% at 9-10 weeks.

Table 1: Demographic data and duration of disease of the studied population, (n=100).

Variables	N	Percentages (%)
Age (In years)		
15-20	38	38
21-25	41	41
26-30	21	21
Gender		
Male	53	53
Female	47	47
Race		
White	39	39
Black	31	31
Others	30	30

Table 2: Treatment progression of the studied population.

Treatment time (Weeks)	Improvement on IGA	Percentages (%)
1-2	5	5
3-4	13	13
5-6	19	19
7-8	28	28
9-10	35	35

Table 3: Reduction in the growth of *Propionibacterium acnes* measured on a logarithmic scale.

Contact time (hours)	FAC log reduction	5% BP log reduction
0-3	0.03	0.04
3-6	2.45	2.61
6-9	>3.66	>3.66
9-12	>3.66	>3.66

Table 3 presents the reduction in the growth of *Propionibacterium acnes*, measured on a logarithmic scale, in response to different contact times with a combination of substances. The contact time intervals (0-3 hours, 3-6 hours, 6-9 hours, and 9-12 hours) are associated with varying levels of logarithmic reduction in both free active chlorine (FAC) and 5% benzoyl peroxide (BP). Notably, the data reveals a progressive increase in log reduction values from 0-3 hours to 3-6 hours. For the subsequent intervals (6-9 hours and 9-12 hours), the log reduction values exceed 3.66, indicating a substantial reduction in *Propionibacterium acnes* growth.

Table 4: Characteristics of study retinoids.

Drug	Mol weight (g/mol)	pka
Tazarotene	351.5	1.23
Trifarotene	459.5	3.97
Tamibarotene	351.4	3.69
Adapalene	412.5	4.23
Isotretinoin	300.4	4.19

Table 4 provides key information on the retinoids, including their molecular weight in grams per mole (g/mol) and pKa values. Tazarotene, with a molecular weight of 351.5 g/mol and a pKa of 1.23, is characterized by a relatively low acidity. Trifarotene, having a molecular weight of 459.5 g/mol and a pKa of 3.97, demonstrates intermediate properties. Tamibarotene, with a molecular weight of 351.4 g/mol and a pKa of 3.69, shares similarities with tazarotene. Adapalene, with a molecular weight of 412.5 g/mol and a pKa of 4.23, exhibits higher acidity. Isotretinoin, with a molecular weight of 300.4 g/mol and a pKa of 4.19, represents another distinct profile.

Table 5: Patient's reaction to the combination of doxycycline plus trifarotene.

Type	N	Percentages (%)
Mild	21	21
Moderate	17	17
Good	36	36
Excellent	26	26

Table 5 presents a comprehensive overview of patients' reactions to the combination treatment of doxycycline and trifarotene in managing acne. Data categorize the responses into different types, including mild, moderate, good, and excellent. Frequency column details the number of patients exhibiting each type of reaction, while percentages column provides proportional representation within studied population. Notably, 36% of patients reported a 'good' response, making it the most frequently observed reaction, followed by 'excellent' at 26%.

Table 6: Acne severity distribution over treatment weeks.

Variables	N	Percentages (%)
1-2 week		
Mild	45	45
Moderate	55	55
3-4 week		
Mild	40	40
Moderate	60	60
5-6 week		
Mild	37	37
Moderate	63	63
7-8 week		
Almost clear	27	27
Mild	24	24
Moderate	49	49
9-10 week		
Almost clear	59	59
Mild	29	29
Moderate	12	12

Table 6 illustrates the distribution of acne severity among patients over different treatment weeks in the study evaluating the effectiveness of the combination therapy

of doxycycline and trifarotene. The table is organized by treatment weeks, from 1-2 weeks to 9-10 weeks, and provides the frequencies and percentages of patients experiencing mild, moderate, or almost clear skin. The data reveal a dynamic pattern in the response to treatment, with the percentage of patients with almost clear skin increasing over time.

DISCUSSION

This series of cases highlights the positive outcomes in terms of efficacy and safety achieved through the use of trifarotene 0.005% cream, either alone or in conjunction with doxycycline, for the management of facial and truncal AV in individuals with darker skin experiencing moderate or severe AV. In all instances, the administration of trifarotene 0.005% cream, with or without doxycycline, was well-tolerated, eliciting only mild or moderate side effects. In our study, the age distribution reveals that a significant portion of participants falls within the 15-25 age range, with 38.00% aged 15-20 and 41.00% aged 21-25. Regarding gender, the study comprises 53.00% male and 47.00% female participants. The racial breakdown shows 39.00% White, 31% Black, and 30.00% from other racial backgrounds. In other study we see, approximately 56% of acne patients are estimated to experience truncal acne, with a slightly higher prevalence in males (55% compared to 46%). Contrary to previous beliefs associating it mainly with males, back acne has been revealed to be prevalent in females as well.[14,15] In our study, we highlighted that 5.00% of participants experienced improvement during the initial 1-2 weeks, with a consistent increase in improvement percentages observed at subsequent intervals: 13.00% at 3-4 weeks, 19.00% at 5-6 weeks, 28.00% at 7-8 weeks, and a significant 35.00% at 9-10 weeks. In other study we see, in two extensive Phase III trials, encompassing a combined total of 2,420 patients with moderate acne, trifarotene monotherapy demonstrated success in IGA rates, with 42.3% and 29.4% achieving clear/almost clear status plus at least a 2-grade improvement by the study endpoint at week 12 ($p<0.001$ compared to the vehicle). It is important to note the restricted comparability of existing studies in the context of severe acne.[16,17] The combination of trifarotene plus oral doxycycline was a safe and effective treatment regimen in subjects with severe acne. There were highly significant and clinically relevant improvements in both IGA and lesion counts after 12 weeks of active treatment.[18] In our study, tazarotene, with a molecular weight of 351.5 g/mol and a pKa of 1.23, is characterized by a relatively low acidity. Trifarotene, having a molecular weight of 459.5 g/mol and a pKa of 3.97, demonstrates intermediate properties. In a study we see, Deposition of tretinoin in the epidermis and dermis from the tretinoin 0.05% micronized formulation is reported to be 3-fold greater than from the tretinoin microsphere 0.1% gel (21% and 3% compared to 7% and 1% respectively).[19] In our study, 36% of patients reported a 'good' response, making it the most frequently observed reaction, followed by 'excellent' at 26%. In a series of cases, four out of 5 subjects demonstrated nearly 100% adherence. The first case involves an Asian female with skin phototype III, exhibiting a slightly lower adherence of 85% to topical trifarotene 0.005% cream. However, the only observed local tolerability reaction was moderate erythema at week 4. Generally, signs and symptoms of tolerability are mild and transient, occurring within the initial 4 weeks of treatment.[20-22]

Limitations

One limitation of the study is the single-arm design, which lacks a comparative group for a more robust evaluation of treatment efficacy. Additionally, relatively small sample size of 100 individuals may impact generalizability of findings to broader populations.

CONCLUSION

In conclusion, this observational study investigating a novel therapeutic regimen combining doxycycline and trifarotene for the treatment of moderate facial and truncal AV demonstrates a comprehensive approach to address variations in clinical response among individuals with diverse skin types. The meticulous adherence to established practices, stratified randomization, and utilization of a fourth-generation topical retinoid, trifarotene, underscore the study's rigor. The results, assessed through the IGA, highlight promising efficacy and safety profiles, providing valuable insights for optimizing acne management strategies in a diverse patient population.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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