

## A Study of the Efficacy of Doxycycline plus Trifarotene in the Treatment of Moderate to Severe Acne Vulgaris

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### Abstract

### Original Research Article

**Introduction:** Acne is a common cutaneous disease affecting the pilosebaceous apparatus, in which there is hyperkeratinization, excessive sebum production, follicular colonization with *Propionibacterium acnes* & inflammation. It manifests as comedones, papules, pustules, nodules & cysts on the face, neck, and trunk. Epidemiologic studies indicate acne affects approximately 9.4% of the global population, ranking it as the eighth most prevalent disease worldwide. It is a common skin condition of the face and trunk that negatively impacts the quality of life. **Objectives:** We evaluated the efficacy of oral doxycycline in combination with topical trifarotene in the treatment of moderate to severe acne vulgaris. **Methods:** This was an interventional study for 12-week duration to see the treatment outcome in moderate & severe acne patients. This study was carried out at the Dept. of Dermatology & Venereology, Enam medical college Hospital, Savar, Dhaka, Bangladesh from January 2022 to September 2022. We evaluated a new therapeutic regimen: Doxycycline 100 mg (Oral) once daily during dinner with food and enough water, 21 days / month, for three consecutive months along with topical Trifarotene 0.005% w/w once daily at night after proper cleansing for the same duration. Acne severity was graded using Investigator Global Acne Assessment Scale (IGAS). **Results:** A total of 96 patients with moderate to severe acne were treated & among them 85 completed this study. Out of these 85, 15 are males & 70 are females. There was a marked improvement in IGAS with marked reduction in the number of inflammatory and non-inflammatory lesions between the beginning of the study and through follow up visits. Clinical response to Doxycycline Plus Trifarotene was excellent in 15%, good in 68%, moderate in 14% and mild in 3% and satisfaction to treatment was 22% very satisfied, 60% satisfied and 17% somewhat satisfied. Side effects were low and only 2.1% of cases had mild irritation. **Conclusion:** Doxycycline plus Trifarotene is effective and safe in the treatment of AV with minimal side effects.

**Keywords:** Doxycycline, Trifarotene, Acne Vulgaris.

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## INTRODUCTION

Acne vulgaris is a common skin disease that manifests as comedones, papules, pustules, nodules and cysts on the face, neck, and trunk. Epidemiologic studies indicate acne affects approximately 9.4% of the global population, ranking it as the eighth most prevalent disease worldwide [1]. Up to 85% of adolescents experience acne and while often mistakenly perceived as a disease limited to teenagers, many adults are affected as well [2]. The psychosocial effects of acne are well documented and include negative impacts on self-perception, social functioning, and mental health [2,3]. Furthermore, any severity of acne can result in

long lasting scarring, a risk that tends to increase as disease severity worsens [4, 5]. Current treatment options for acne includes interventions with topical medications in mild-to moderate disease with the addition of systemic medications as severity increases [6]. Some options include tretinoin, azelaic acid, benzoyl peroxide, sulfur, salicylic acid, resorcinol, or routine face washing with mild soap [7]. Antibiotics that can be used for acne include tetracycline, doxycycline, erythromycin, minocycline, azithromycin and clindamycin [8-13]. Oral antibiotics are frequently prescribed to treat severe acne and are recommended by acne treatment guidelines, with the precaution to limit

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the period of treatment to the minimum necessary to reduce the risk of antibiotic resistance [14, 15]. Doxycycline is a useful antibiotic in acne due to its antibacterial and anti-inflammatory effects. The recommended treatment consists of 1 capsule per day (100 mg Doxycycline) for 3 months. Long antibiotic treatments in acne patients produce unwanted side effects [16, 17]. Doxycycline has an overall favourable efficacy and safety profile; however, current acne recommendations suggest limiting duration of use to minimize risks for antimicrobial resistance [18, 19]. Trifarotene is a new first-in-class fourth-generation topical retinoid that has been uniquely studied in the treatment of both facial and truncal acne. Through selective agonism of retinoic acid receptor (RAR)-gamma, the most predominant RAR isotype in the epidermis, trifarotene exerts more targeted, skin-specific effects than earlier generation retinoids [20,21]. The current interventional study was designed to provide information about the efficacy and safety of doxycycline plus trifarotene in patients with moderate to severe facial acne.

## MATERIALS AND METHODS

This was a prospective open labeled interventional study carried out at the Dept. of Dermatology & Venereology, Enam Medical College Hospital, Savar, Dhaka, Bangladesh from January 2022 to September 2022. We evaluated a new therapeutic regimen: Doxycycline 100 mg (Oral) once daily during dinner with food and enough water, 21 days/month, for three consecutive months along with topical Trifarotene 0.005%w/w once daily at night after proper cleansing for the same duration.

The patients were selected from the OPD of dermatology and venereology department provided that the patients have not received any medication, either topical or systemic treatment for AV during the previous 2 weeks. Patients were evaluated by careful history taking, general examination, complete dermatological examination including type of acne and counting of inflammatory and non-inflammatory acne lesions, after taking informed written consents. Patients, allergic to doxycycline, pregnant and lactating women or women who are planning for pregnancy and patients on isotretinoin treatment within 3 months before the beginning of the study were excluded from this study. Although the importance of completing the entire clinical study was explained to the subjects, any subject was free to discontinue his or her participation in the study at any time and for whatever reason, specified or unspecified and without prejudice. No constraints were imposed on the subject and when appropriate, a subject would have been treated with other conventional therapy when clinically indicated.

Acne severity was graded using Investigator Global Acne Assessment Scale (IGAS), along with lesional photography for each patient before the start of treatment with Doxycycline plus Trifarotene. The severity of acne was determined as five grades (clear, almost clear, mild, moderate and severe), depending upon the number of inflammatory and non-inflammatory lesions.

The treatment regimen consisted of Doxycycline 100 mg (Oral) once daily during dinner with food and enough water, 21 days / month, for three consecutive months along with topical Trifarotene 0.005%w/w once daily at night after proper cleansing for the same duration.

The patients were re-evaluated at 2, 4, 8 and 12 weeks of treatment (the end of therapy), using IGAS, lesional photography together with recording satisfaction of the patient by 4 points scale (as 1=not satisfied, 2=somewhat satisfied, 3=satisfied and 4=very satisfied) Patient's response to treatment was recorded and classified using 6 points scale into excellent, good, moderate, mild, unchanged and worse [14]. Safety and patient's compliance were recorded at each follow up visits.

### Statistical analysis

All data were collected by a structured questionnaire containing all the variables. Efficacy, safety and vital signs were summarized by analysis visit. Data were checked, entered and analysed by using (SPSS version 20) software computer package. Data were expressed as mean  $\pm$  standard deviation (SD) for quantitative variables, number and percentage for categorical variables. P value<0.05 indicated significant results.

## RESULTS

A total of 96 patients with moderate to severe acne were treated & among them 85 completed this study. Out of these 85, 15 (17.7%) are males & 70 (82.3%) are females. Their ages ranged between 14-29 years (mean=19.45  $\pm$  2.55). The duration of acne ranged from 1 month to 3 years with a mean  $\pm$  SD (1.85  $\pm$  0.7).

The Demographic data and duration of disease of the studied are presented in (Table 1 & 2).

**Table-1**

Variable	(N=85)
Age (years):	14-29
Mean $\pm$ SD	19.45 $\pm$ 2.55
Duration (years):	1month – 3y
Mean $\pm$ SD	1.85 $\pm$ 0.7

**Table-2**

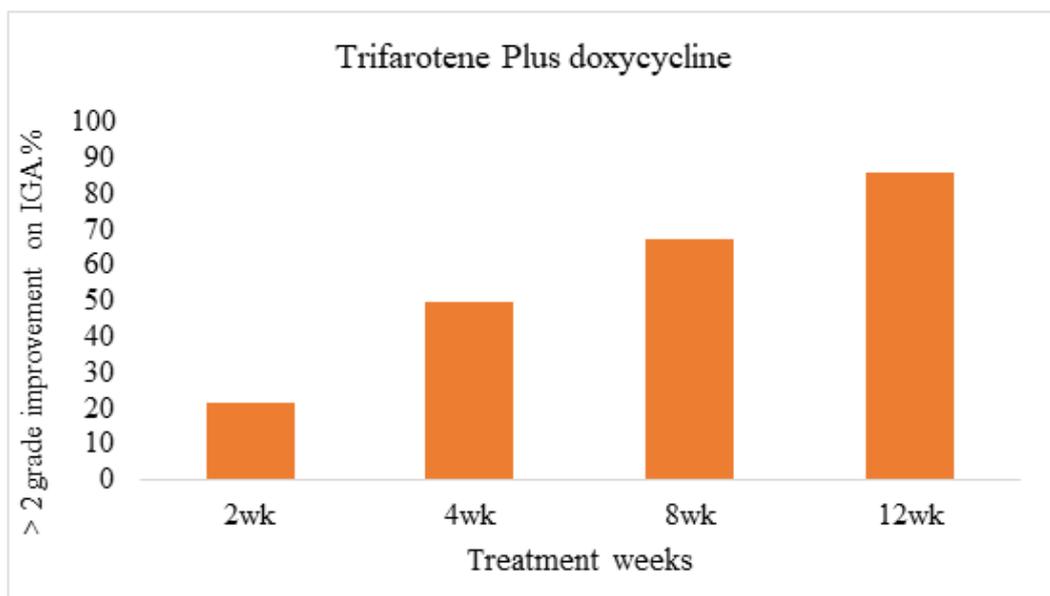
Variable	No	%
Male	15	17.7
Female	70	82.3

**Table-3: Investigator global assessment score (IGAS) & P value at different follow up times (Base line, 2<sup>nd</sup> week 4th week, 8th week & 12th week) in studied cases.**

Variable	(N=85)	%	P value
IGAS: Base line			
Moderate	57	67	0.02
Severe	28	33	
IGAS: 2 <sup>nd</sup> week			
Mild	18	21.2	<0.001
Moderate	45	52.9	
Severe	22	25.8	
IGAS: 4th week			
Mild	42	49.5	<0.001
Moderate	31	36.5	
Severe	12	14	
IGAS: 8th week			
Almost clear	20	23.5	<0.001
Mild	57	67	
Moderate	8	9.5	
IGAS: 12th week			
Almost clear	29	34	<0.001
Mild	52	61	
Moderate	4	5	

As regards IGAS at different follow up times in studied patients, at the beginning of treatment 33% of the cases were suffering from severe degree, 67% have moderate acne. After 12 week no severe cases were found and only 5% were moderate, 61% were mild and

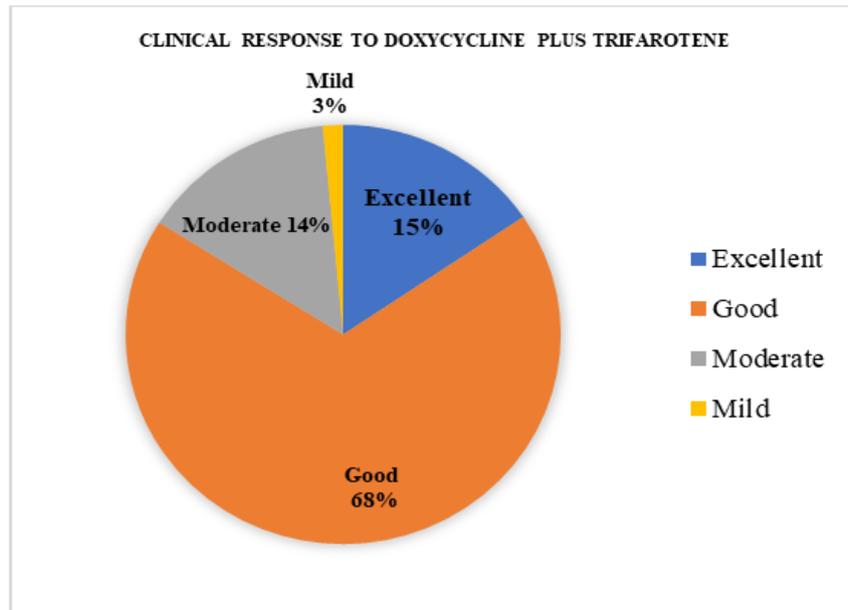
34% of the cases became almost clear. There were statistically significant differences in IGAS between base line and all other follow up weeks in severity of disease among the studied patients (Table-3).



**Fig-1: Proportion of subjects with > 2 grade improvement on IGA.**

**Table-4: Subject disposition.**

Variables	N=96
Subjects randomized and treated who completed this study	85 (88.5)
Subjects randomized and treated who discontinued this study	11 (11.5)
Adverse event	2 (2.1)
Lost to follow-up	4 (4.2)
Withdrawal by parent/guardian	1 (1.04)
Withdrawal by subject	4 (4.2)
Other	0 (0.0)



**Fig-2: Clinical response to Doxycycline Plus Trifarotene.**

**Table-5: Satisfaction among the studied cases.**

Variables	Cases (N=85)	
	N	%
Satisfaction:		
1. Not satisfied	0	0
2. Somewhat satisfied	15	17
3. Satisfied	51	60
4. Very satisfied	19	22

There was no statistically significant relation between duration of acne and IGAS, response to treatment or satisfaction. No statistically significant difference between males and females as regard response to treatment ( $P > 0.05$ ). The photo documentations of clinical improvement from baseline to Week 12 in subjects treated with once-daily doxycycline plus trifarotene are presented in Figures 3 & 4.



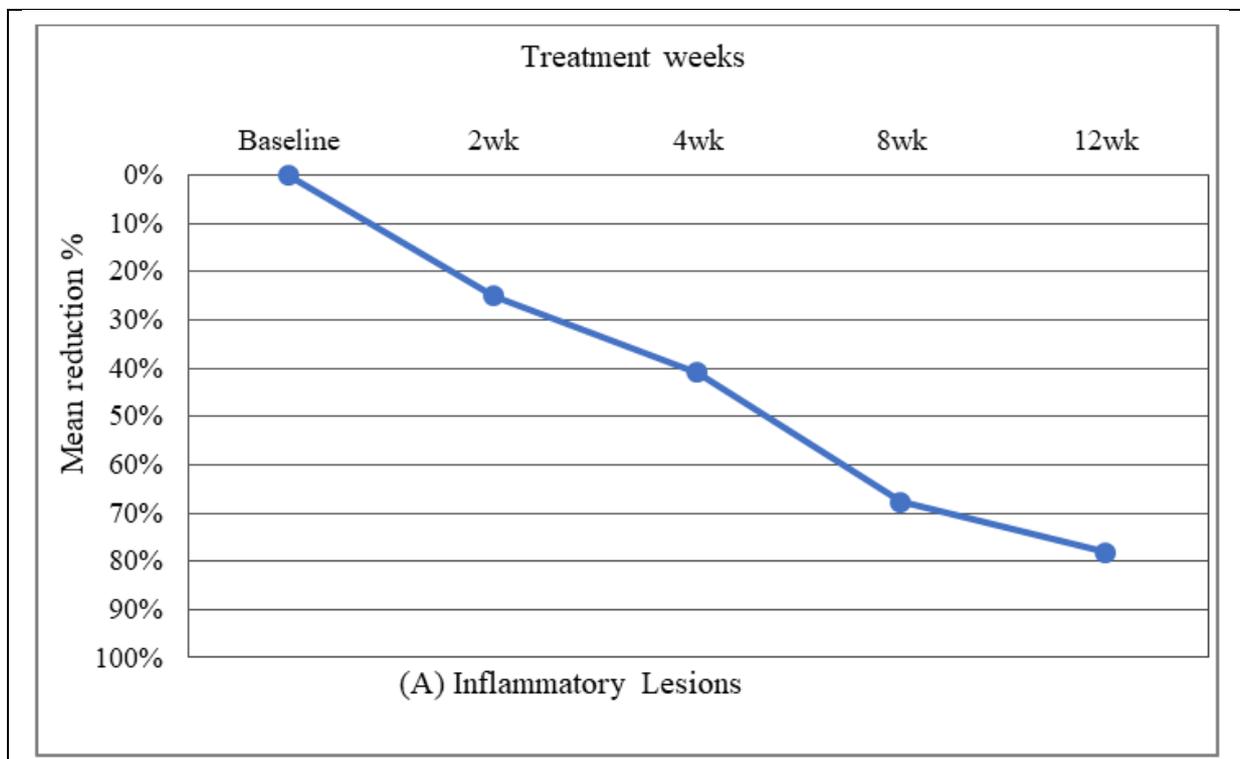
**Fig-3: Moderate acne (before & after photograph).**



**Fig-4: Severe acne (before & after photograph).**

From baseline to week 12, patients treated with Doxycycline plus trifarotene showed mean percent reduction of total lesions by 73.8%. There was mean reduction of 78.1% in inflammatory lesions and 69.5% in non-inflammatory lesions after 12 week of treatment

with Doxycycline plus trifarotene. Mean percent reduction of inflammatory lesions were more as compared to non-inflammatory lesions as seen in figure below:



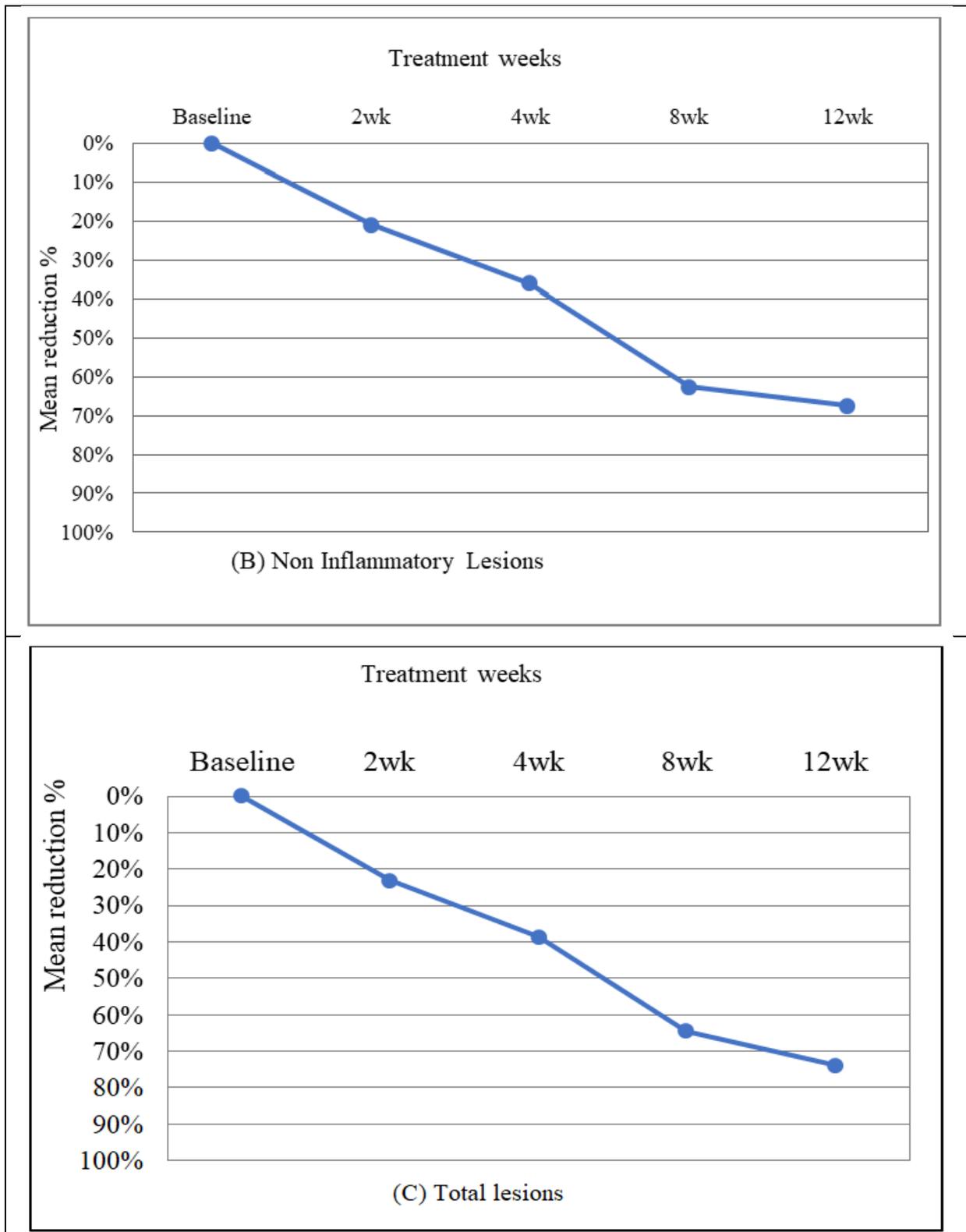


Figure-5(A, B, C): Mean percent change in inflammatory lesions, non-inflammatory lesions and total lesions count.

## DISCUSSION

Acne vulgaris is an inflammatory disease of pilosebaceous apparatus. It is clinically characterized by comedones, papules, pustule, nodule, cyst and

occasional scarring. Hyperkeratinization, excessive sebum & inflammatory mediators production, follicular colonization with *Propionibacterium acnes* are the factors for pathogenesis of acne [22]. Acne has a well-established link to depression, anxiety, and a

diminished quality of life [23]. According to the Global Burden of Disease Study 2010, acne vulgaris is the eighth most common cutaneous ailment, with a global prevalence of 9.38% [24]. Retinoids are the core of topical therapy for acne because they are comedolytic, cure the antecedent microcomedone lesion and are anti-inflammatory. According to the AAD recommendations, they also allow for the maintenance of clearance [25, 26]. There are relatively few published studies reporting the efficacy of combining oral doxycycline & topical trifarotene treatment regimens in moderate to severe acne; thus, there is a need for evidence-based information concerning treatment options in this patient population [27]. As research is still evolving in the case of trifarotene, data continue to pour from all over the world. However, trifarotene has been accepted well by patient groups and dermatologists globally. 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 [28]. Stein-Gold *et al* have reported that both acne lesion types and lesion quantities should be considered in an overall assessment of acne severity [29]. Oral Isotretinoin is an effective treatment for severe acne, but it has side effects that some patients consider intolerable and that can sometimes persist after treatment cessation [30]. A 52-week study (n=453) showed trifarotene has good safety and tolerability, with adverse effects that occurred in approximately 10% of subjects, usually in the first three months of therapy, were mostly cutaneous, and were non-serious [31]. Oral antibiotics are frequently prescribed in a survey of general practitioners in Ireland (n=298), 17% indicated that they would prescribe isotretinoin therapy, citing long wait times for dermatology consultation. The remaining 83% of respondents who did not prescribe isotretinoin gave the following as barriers to use: medical-legal concerns (61%), lack of awareness that they could prescribe isotretinoin (55%) and lack of familiarity in managing patients on isotretinoin (41%) [32]. The other study by Landis reported that prescribing and monitoring protocols have wide variations among clinicians, suggesting that much could be done to optimize use of isotretinoin. However, until change occurs, it is vital for clinicians to have alternatives to isotretinoin therapy for patients with severe acne. An acne flare may occur at the beginning of oral retinoid treatment, providing a rationale for using a topical retinoid before initiating therapy. In addition, isotretinoin monitoring can be troublesome for both clinicians and patients [33]. The potential for teratogenicity has led to creation of stringent pregnancy prevention programs in many countries, such as the somewhat controversial risk evaluation and mitigation program named iPLEDGE in the United States. [34]. Two large-scale Phase III trials involving a total of 2,420 patients with moderate acne showed trifarotene monotherapy achieved investigator global assessment

(IGA) success (clear/almost clear plus at least 2-grade improvement) rates of 42.3% and 29.4% by study endpoint at week 12 (P<0.001 vs. vehicle). Despite the limited comparability of existing studies in severe acne, published data from Tan *et al* [23] Dreno *et al* [35] and Gold *et al* [36] support the conclusions of this study that the combination of a retinoid with oral doxycycline is an appropriate regimen for moderate & severe acne. In our study the combination of trifarotene plus oral doxycycline was a safe and effective treatment regimen in subjects with moderate to severe acne. There were highly significant and clinically relevant improvements in both IGA and lesion counts after 12 weeks of active treatment. Patients were instructed properly about applying medication and the use of cleanser and moisturizer also may have contributed in clinical response.

## CONCLUSION

Oral antibiotic combined with topical retinoid are an efficacious therapy for moderate to severe acne, such as Doxycycline plus Trifarotene are effective and safe in the treatment of AV with minimal side effects. This evaluation will encourage us to apply the treatment regimen in a larger scale.

**Conflict of Interest:** None.

**Source of Fund:** Nil.

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