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# Efficacy and Tolerability of a Fixed-Dose Benzoyl Peroxide 5% and Clindamycin 1% Gel Alone or in Combination with Oral Vitamin A 50.000 IU in the Treatment of Mild-to-Moderate Acne: A Prospective, Randomized, Assessor Blinded Trial

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**Abstract**

**Introduction & Objectives: Benzoyl peroxide (BPO) is commonly used alone or in combination with retinoids or antibiotics as first line treatment in acne vulgaris (AV). BPO-based topical anti-AV products are effective however, often, the skin tolerability profile is not optimal due to skin irritation and skin dryness commonly observed during treatment. It is frequently needed to combine an appropriate dermo cosmetic approach to restore the function of the skin barrier. The fixed-dose combination of BPO with clindamycin (BPO-Cli) has demonstrated to be very effective and well tolerated in the treatment of AV. Oral vitamin A (retinol) has shown to improve AV lesions mainly in non-controlled observational studies with a good skin tolerability. Some data suggest that oral Vitamin A could also have beneficial effects on gut microbiome. So far, no controlled data regarding an "In&Out" strategy using BPO-Cli topical product and oral Vitamin A have been conducted in AV treatment. We evaluated and compared the efficacy and tolerability of BPO-Cli gel alone or in combination with oral Vitamin A in subjects with mild-to-moderate AV. In addition, as secondary endpoint, we evaluated the effect of combination therapy on gut microbiome by mean of Trimethylamine N-Oxide (TMAO) serum measurements.**

**Materials & Methods: In a randomised, prospective, assessor-blinded trial a total of sixty subjects (10 men and 50 women, mean age: 24 years) with AV were enrolled in an 8-week trial, after their informed written consent. Thirty subjects were allocated to BPO-Cli gel treatment (one application per day in the morning) (Group A) and thirty subjects were allocated to**

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**BPO-Cli gel and Vitamin A oral supplementation (50.000 IU) once daily (Group B). The primary endpoint was the evolution of Global Acne Grading System (GAGS) assessing AV lesions number and type (with a score of 0 representing no lesions, 1-18 mild, 19-30 moderate, and >31 severe and very severe acne). GAGS score was evaluated at baseline and after 8 weeks by an investigator unaware of treatment allocation. As indirect parameter of gut microbiota we also measured serum TMAO level in group B subjects at baseline and after treatment.**

**Results: All subjects concluded the 8-week treatment period. No severe adverse events were registered in both groups. At baseline the GAGS score was 26.2 ± 3.0 in Group A and 25.9 ± 2.6 in Group B. After 8-week of treatment Group A shown a percentage reduction of GAGS in comparison with baseline values of -40%. In the Group B the percentage reduction was -56%. At week 8, the GAGS values were significantly lower (p=0.0001) in Group B (11.4 ± 2.8) in comparison with Group A (15.8 ± 3.0) with an absolute difference of -4.37 points (95% CI: -5.9 to -2.8). At week 8, the percentage of subjects with a GAGS score <18 was 66.7% (20 out 30) in Group A and 96.7% in Group B (29 out of 30) (P=0.0056; Fisher exact test). At baseline TMAO serum levels were 3 ± 2. The treatment with oral vitamin A reduced TMAO serum level to 1.9 ± 1.8 (representing a 37% reduction) (P=0.024; paired t-test).**

**Conclusion: The combination of BPO-Cli with oral Vitamin A has shown to be more effective in comparison with the topical treatment alone in the treatment of mild-moderate AV. Oral vitamin A seems also able to positively modulate in acne subjects gut microbiome, probably trough a decrease of TMA producing bacteria (i.e. Proteobacteria). The combination was also very well tolerated.**

**Keywords:** ***Acne; Vitamin A; Clindamycin; Assessor-blinded trial; Gut microbiome***

## 1. Introduction

Acne vulgaris (AV) is a common chronic inflammatory skin disease affecting pilosebaceous rich regions [1]. Four are the main pathogenetic factors of AV: excessive sebum production, follicular hyperkeratinisation, *Cutibacterium acnes* proliferation and finally inflammation response [2]. In mild to moderate forms international guidelines indicate combination therapy with antibacterial agents like benzoyl peroxide and retinoid or topical antibiotics, like clindamycin as first treatment line [3]. Benzoyl peroxide (BPO) is commonly used alone or in combination with retinoids or antibiotics as first line treatment in acne vulgaris (AV) [4]. BPO alone or in combination with topical retinoids could alter the skin barrier function especially during the very first weeks of treatment [5]. During the first weeks of treatment with BPO alone or combined with retinoids can increase by 60% the Trans Epidermal Water Loss (TEWL) [6]. On the contrary BPO combined with topical antibiotics are effective and better tolerated than fixed combination of BPO and retinoid [7]. However, often, also with this combination the skin tolerability profile is not optimal due to skin irritation and skin dryness commonly observed during treatment. It is frequently needed to combine an appropriate dermo cosmetic approach to restore the function of the skin barrier [8]. The fixed-dose combination of BPO with clindamycin (BPO-Cli) has demonstrated to be very effective and well tolerated in the treatment of AV. This combination has demonstrated to reduce significantly total acne lesion by 27% in comparison with placebo [9]. These data however suggest that there is margin of improvement in term of lesion count reduction. Oral vitamin A (retinol) has shown to improve AV lesions mainly in non-controlled observational studies with a good skin tolerability [10]. In addition, oral vitamin A can positively modulate gut microbiome [11]. It is well known in fact that alteration of gut microbiome has been extensively

demonstrated in subject with acne [12]. The assessment of gut microbiome using faecal samples, especially in controlled clinical trials, could be difficult and very expensive to perform with low reproducibility [13]. Quite recently an indirect evaluation of gut microbiome was performed measuring different metabolic serum markers for example trimethylamine N-oxide (TMAO) [14]. Gut dysbiosis, could be characterized by increase production levels of Trimethylamine (TMA) [15]. TMA is then metabolized to TMAO which is excreted in the urine [16]. Therefore, serum levels of TMAO is now considered a parameter of gut dysbiosis. High serum levels of TMAO are correlated with gut dysbiosis in particular high relative abundance of Proteobacteria phylum [17]. In AV subjects has been demonstrated that this phylum has a greater relative abundance in comparison with healthy subjects [18]. So far, no controlled data regarding an "In&Out" strategy using BPO-Cli topical product and oral Vitamin A have been conducted in AV treatment evaluating clinical efficacy and modulation of gut microbiome.

## 2. Study Aim

In the current trial, we evaluated and compared the efficacy and tolerability of BPO-Cli gel alone or in combination with oral Vitamin A in subjects with mild-to-moderate AV. In addition, as secondary endpoint, we evaluated, only in subjects randomized to combination treatment, the indirect effect gut microbiome by mean of TMAO serum measurements.

## 3. Materials & Methods

### 3.1 Subjects

This was a monocentre trial conducted in a tertiary university dermatology clinic between September 2023 and February 2024. The study was conducted according to Good Clinical Practices procedures and Helsinki declaration. In a prospective, balanced randomisation, assessor-blinded study a total of sixty subjects (10 men and 50 women, mean age: 24 years) with AV and meeting all inclusion/exclusion criteria were enrolled in an 8-week trial, after their written informed consent. Eligible participants were all adults of both sexes aged 18 or over with mild to moderate acne vulgaris.

Exclusion criteria were the presence of other facial pathologies that interfere with the assessment of acne, allergy to one or more components of the topical formulation used, pregnancy or breastfeeding, current treatment or discontinuation for less than 2 months of oral isotretinoin, or for less than 1 month in the case of oral antibiotics and estrogen, or for less than 2 weeks in the case of any topical treatment. Thirty subjects were allocated to BPO-Cli gel treatment (one application per day in the morning) (Group A) and thirty subjects were allocated to BPO-Cli gel and Vitamin A oral supplementation (50.000 IU) once daily (Group B). The randomization list was generated by a dedicated computer program.

### 3.2 Study outcomes

The primary endpoint was the evolution of Global Acne Grading System (GAGS) assessing AV lesions number and type (with a score of 0 representing no lesions, 1-18 mild, 19-30 moderate and >31 severe and very severe acne). GAGS score was evaluated at baseline and after 8 weeks by an investigator unaware of treatment allocation. As indirect parameter of gut microbiome we also measured serum TMAO level in group B only subjects at baseline and after 8 weeks of treatment.

### 3.3 Statistical analysis

Statistical analysis was performed using GraphPad statistical software ver. 5.0 (La Jolla, CA, USA). The primary endpoint of the trial was the evolution and comparison of GAGS score from baseline to week 8 (end of treatment). The Wilcoxon and ANOVA tests were used for the analysis of the study outcomes. Differences were considered significant when $P<0.05$. The efficacy analysis evaluated the hypothesis if the combination group would be able to significantly reduce the GAGS score (the primary endpoint of the study) in comparison with the topical treatment alone. Therefore, sample size calculation was performed on the hypothesis that the combination treatment group could reduce the GAGS score, in comparison with topical treatment alone, with an effect size of at least 0.8.

With an alpha value of 0.05 and a power of 95%, a total of at least 30 subjects per arm should be enrolled to detect this difference. The sample size was calculated using G-Power statistical software version 3.9 (Kiel, Germany). The analysis was performed based on the intention-to-treat principle, using the Last-Observation-Carried- Forward (LOCF) methods. We summarized continuous variables by mean ± standard deviation (SD), calculating also the 95% Confidence Intervals (CI) for the observed differences.

## 4. Results

TABLE 1 summarizes the subjects' characteristics at baseline. All subjects concluded the 8-week treatment period. No severe adverse events were registered in both groups. FIG. 1 shows the study flow.

TABLE 1. **Demographics and baseline characteristics.**

| | **Group A**<br>**BPO-Cli gel**<br>**(n=30)** | **Group B**<br>**BPO-Cli gel + Vit A**<br>**(n=30)** |
|---|---|---|
| **Age (mean ± SD)** | 24.7 ± 5.1 | 23.4 ± 4.9 |
| **Sex**<br>Female<br>Male | <br>25 (83%)<br>5 (17%) | <br>25 (83%)<br>5 (17%) |
| **GAGS (mean ± SD)** | 26.2 ± 3.0 | 25.9 ± 2.6 |

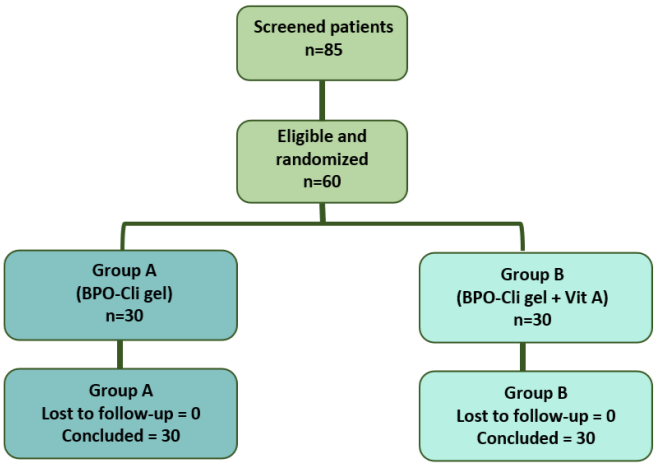


FIG. 1. **Study flow.**

At baseline the GAGS score was 26.2 ± 3.0 in Group A and 25.9 ± 2.6 in Group B. After 8-week of treatment Group A shown a percentage reduction of GAGS in comparison with baseline values of -40%. In the Group B the percentage reduction was -56%. At week 8, the GAGS values were significantly lower (p=0.0001) in Group B (11.4±2.8) in comparison with Group A (15.8±3.0) with an absolute difference of -4.37 points (95% CI: -5.9 to -2.8) (FIG. 2). At week 8, the percentage of subjects with a GAGS score <18 was 66.7% (20 out 30) in Group A and 96.7% in Group B (29 out of 30) with an absolute difference of 30% (95% CI 20-40%) (P=0.0056; Fisher exact test). In Group B at baseline TMAO serum levels were 3 ± 2. The treatment with oral vitamin A reduced TMAO serum level to 1.9 ± 1.8, representing a 37% reduction (p=0.024; paired t-test) (FIG. 3).

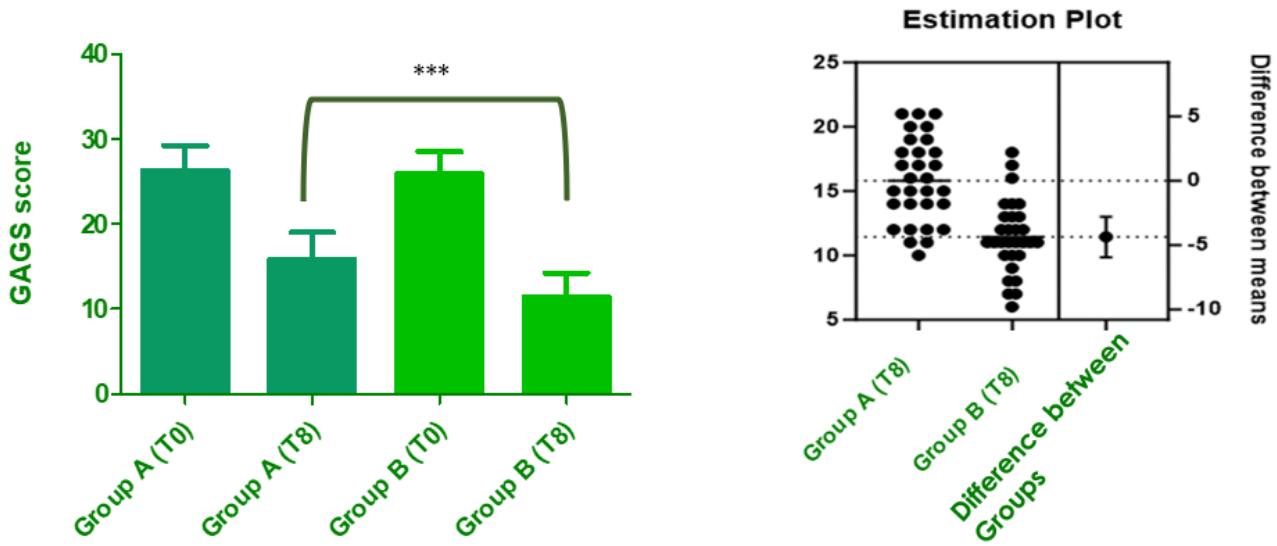


FIG. 2. **a) GAGS score evaluated at Baseline (T0) and after 8 weeks (T8) in Group A (BPO-Cli gel) and Group B (BPO-Cli gel + Vit A); b) absolute difference in GAGS score between groups, ***p=0.0001.**

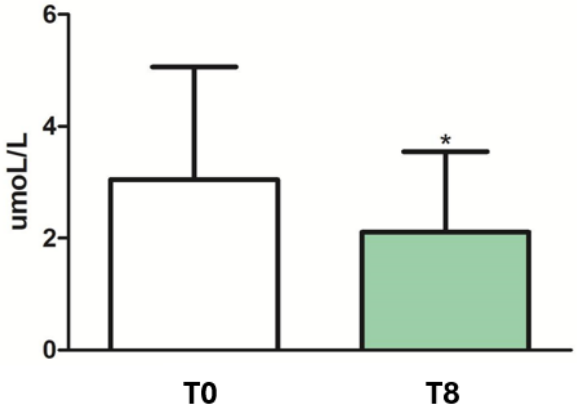


FIG. 3. **TMAO serum level measure in Group B (BPO-Cli gel + Vit A) at Baseline (T0) and after 8 weeks (T8), *p=0.024.**

In FIG. 4 are reported photographs of some patients in Group A (BPO-Cli gel) and Group B (BPO-Cli gel + Vit A) taken at baseline and after 8 weeks.

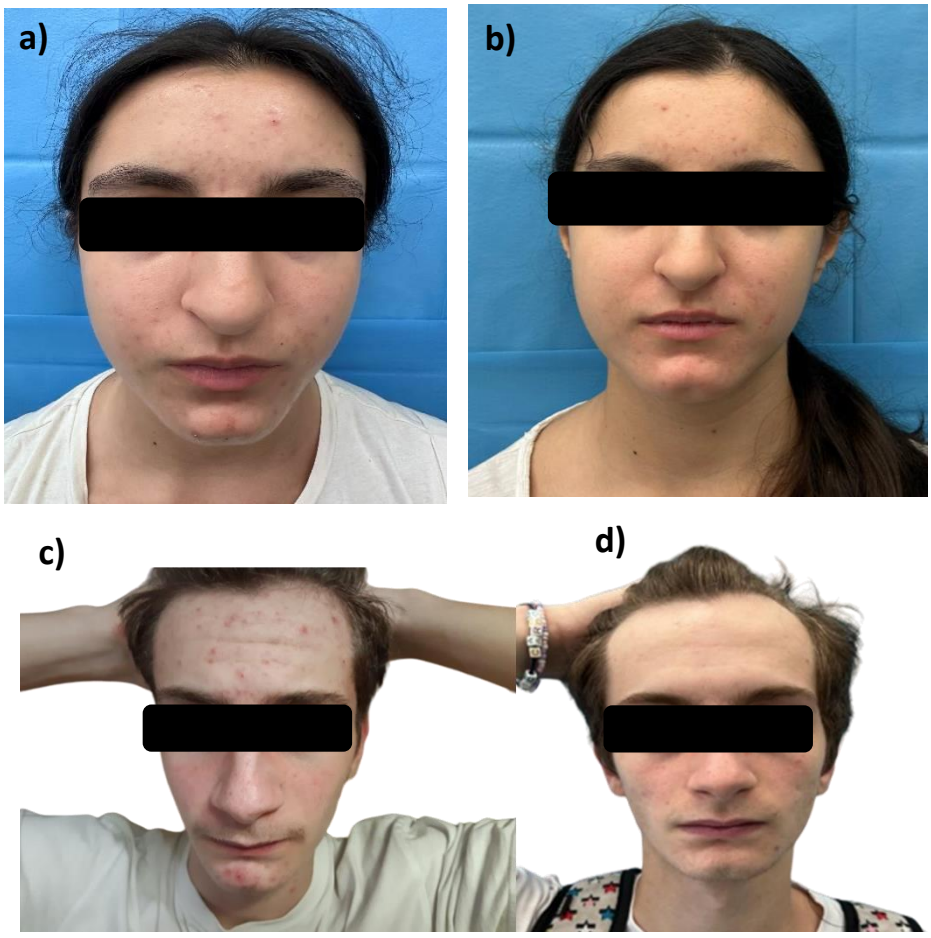


FIG. 4. **Representative photographs of a patient in Group A (BPO-Cli gel) taken at baseline (a) and after 8 weeks (b) compared to photographs of a patient in Group B (BPO-Cli gel + Vit A) taken at baseline (c) and after 8 weeks (d).**

## 5. Discussion

Acne affects 85% of teenagers but is also common in adult subjects [19]. The pathogenesis of this skin disease implies the interaction of several host factors, including the stimulation of sebaceous glands by circulating androgens, dysbiosis of the pilosebaceous follicle microbiome, and cellular immune responses [20]. In addition, other factors such as genetics and diet may also influence the development and progression of acne vulgaris [21]. In the present trial we found that the combination of topical BPO+antibiotic and oral vitamin A is superior to topical treatment alone in term of improvement of acne lesions. Alteration of gut microbiome has been also demonstrated in AV [22]. Gut microbiome has a relevant role in the maintenance of host health [23]. Alteration of gut microbiome can play relevant pathogenetic mechanism in many diseases [24]. Several scientific evidence demonstrated that gut microbiome of acne subjects is different in comparison with subjects without acne showing less microbial diversity [25]. In Acne subjects gut microbiome is altered with a reduction in the phylum of Actinobacteria and an increase of Proteobacteria [26]. Oral retinol (Vitamin A) assumption has positive effect on gut Bifidobacterium (belonging to the Actinobacteria phylum) [27]. Furthermore, plasma retinol level positively correlates with gut Actinobacteria. In the present study we found that oral vitamin A administration reduced significantly TMAO serum levels. Gut dysbiosis with a Proteobacteria phylum prevalence is characterized by an increase in TMAO serum levels [28]. In acne subjects the amount of gut Proteobacteria phylum is increased in comparison with healthy subjects [29]. Low carbon ketogenetic diet in AV subjects has demonstrated to improve acne and, at the same time to reduce TMAO serum levels [30]. Our study supports the hypothesis that combination therapy with topical BPO and antibiotic when associated with oral vitamin A supplementation can offer a greater clinical effect in term of acne improvement with additional positive effect on gut microbiome. Some study limitation must be taken in account in evaluating these results. First, this trial was not double blind. To increase the internal validity however we decided to perform an assessor-blinded evaluation of primary clinical outcomes. The TMAO evaluation was performed only in the group B (topical and oral combination) because it was improbable that the group treated only with topical could have a relevant modification on gut microbiome. Future clinical trials addressing the effect of oral vitamin A on gut microbiome in comparison with standard acne treatments are warranted.

## 6. Conclusion

The combination of BPO-Cli with oral Vitamin A has shown to be more effective in comparison with the topical treatment alone in the treatment of mild-moderate AV. Oral vitamin A seems also able to positively modulate in acne subjects gut microbiota, probably trough a decrease of TMA producing bacteria (i.e. Proteobacteria). The combination was also very well tolerated.

## 7. Founding Source

None

## 8. Conflict of Interest

M.M. and F.C. are employees of Difa Cooper Cantabria Labs which commercialized the products used in the trial. All other authors declare no conflict of interest.

## 9. Data Availability

The data that support the findings of this study are available on request from the corresponding author.

## 10. Informed Consent

Written informed consent for publication of their details was obtained from the patients including images.

## 11. Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work

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