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The efficacy of an oral probiotic associated with a fixed combination of adapalene-benzoyl peroxide in the treatment of acne: a randomized, double-blind, placebo-controlled clinical trial

Eficácia de probiótico oral associado à combinação fixa de peróxido de benzoíla e adapaleno no tratamento da acne: estudo clínico randomizado, duplo-cego, placebo- controlado

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ABSTRACT

Introduction: Acne is a chronic inflammatory disease of the pilosebaceous unit of multifactorial origin, which causes a significant impact on quality of life.

Objective: Clinical trial assessing the superiority of efficacy of a treatment regimen with an oral probiotic associated with a fixed combination of adapalene 0.1% and benzoyl peroxide 2.5% compared to an oral placebo with the same topical treatment in patients with acne.

Methods: This was a randomized, double-blind, placebo-controlled study conducted with 212 patients aged from 12 to 35 years. The study was divided into two phases of 90 days each. In the first phase, patients received treatment with adapalene 0.1% and benzoyl peroxide 2.5% associated with a probiotic (IT), or adapalene 0.1% and benzoyl peroxide 2.5% associated with placebo (CT). In the second phase (90 days), patients received only oral treatment with a probiotic or placebo. Efficacy criteria were: reduced Investigator Global Assessment (IGA) scale to 0 or 1 and reduced lesion count.

Results: There was a significant difference in the proportion of participants with IGA 0 or 1 - the arm receiving the test treatment was superior to the control ($p<0.05$). Both treatments were safe and well tolerated. Conclusion: In light of the evidence on efficacy and safety, treatment with probiotics should be considered as an adjuvant therapy for acne control.

Keywords: Acne vulgaris; Probiotics; Gastrointestinal microbiome

RESUMO

Introdução: *a acne é uma doença inflamatória crônica da unidade pilossebácea de origem multifatorial, que causa um impacto significativo na qualidade de vida.*

Objetivo: *ensaio clínico realizado para avaliar a superioridade de eficácia de um regime de tratamento com probiótico oral associado à combinação fixa de adapaleno 0,1% e peróxido de benzoíla 2,5% comparado ao placebo oral com o mesmo tratamento tópico em pacientes com acne leve a moderada.*

Metodologia: *estudo randomizado, duplo-cego e controlado por placebo, conduzido com 212 pacientes de 12 a 35 anos, sendo 107 do grupo de tratamento-teste e 105 do grupo comparador. Na primeira fase, os pacientes receberam o tratamento com peróxido de benzoíla 2,5% e adapaleno 0,1% associado ao probiótico (IT) ou peróxido de benzoíla 2,5% e adapaleno 0,1% associado ao placebo (CT). Na segunda fase, os pacientes receberam apenas o tratamento oral com probiótico ou placebo. Os critérios de eficácia foram a redução da escala IGA para 0 ou 1 e a contagem de lesões.*

Resultados: *houve diferença significativa na proporção superior de participantes com IGA 0 ou 1 para o grupo de tratamento-teste ($p<0,05$). Ambos os tratamentos foram seguros e bem tolerados.*

Conclusão: *à luz das evidências sobre eficácia e segurança, o tratamento com probiótico deve ser considerado na terapia adjuvante para o controle da acne.*

Palavras-chave: *Acne vulgar; Probióticos; Microbioma gastrointestinal*

Original Article

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INTRODUCTION

It is estimated that acne affects about 9.4% of the global population, and it is one of the most prevalent diseases worldwide,[1] especially in adolescents, affecting 85% of this population.[2] The disease impacts significantly the quality of life and is commonly associated with psychiatric disorders such as low self-esteem, social phobias, and depression.[3]

Acne is a chronic inflammatory disease of the pilosebaceous unit of multifactorial origin, resulting from dysfunction in sebum production, altered infundibular keratinization, inflammation, and bacterial dysbiosis of hair follicles.[4]

Although the exact way in which these processes interact and the order in which they occur in the pathogenesis of acne is still not fully known,[5] recent discoveries about the commensal bacterium *Cutibacterium acnes (C. acnes)* point to the critical role of the balance between its strains in the pathophysiology of the disease. Contrary to previously thought, the proliferation of *C. acnes* does not trigger acne, as acne patients do not harbor more strains in their follicles than normal individuals. Instead, loss of skin microbial diversity, with exaggerated activation of innate immunity, may lead to this chronic inflammatory condition.[6] The role of *C. acnes* in the pathophysiology of acne and the inflammatory basis via innate immunity are two factors that have changed treatment approaches. Thus, inflammation became the hallmark of the disease process, from onset to resolution.[7]

In addition to androgen hormones, recent research has linked insulin and insulin-like growth factor-1 (IGF-1) to the pathophysiological process of acne.[8] IGF-1 is related to increased lipogenesis in the sebaceous gland, regardless of androgens,[9] and also to the release of inflammatory cytokines. It is noted that serum levels of IGF-1 are higher in adults with acne and correlate quantitatively with the severity of the disease.[10] Insulin and IGF-1 activate rapamycin complex 1 (mTORC1) signaling, the regulator key components of anabolism and lipogenesis, while suppressing the metabolic transcription factor FoxO1 activity. FoxO1 is a negative co-regulator of several transcription factors crucial to sebaceous lipogenesis.[11]

Current acne treatments have several limitations, and increasing antibiotic resistance has diminished their effectiveness.[12] Therefore, new effective long-term therapies are needed. Given recent discoveries about the pathophysiology of acne, the loss of diversity of *C. acnes* strains in the skin and the IGF-1 signaling pathway are important targets for new therapies.[13] Considering the effects of probiotics in maintaining intestinal and skin microbiome homeostasis, the effectiveness of using these commensal microorganisms has been investigated in recent clinical studies in acne treatment.[12,14,15]

Inhibitory effects of probiotics on *C. acnes*, mediated by antibacterial proteins and bacteriocin-like inhibitory substances, have been demonstrated, in addition to immunomodulatory effects on keratinocytes and epithelial cells.[12] Furthermore, treatment with probiotics improved the clinical parameters of patients with acne and also reduced significantly IGF-1 expression and increased FOX01 expression, with statistical significance, in a randomized, placebo-controlled study.[15]

The effectiveness of probiotics has also been proven as an adjunct therapy to antibiotic acne treatment. A randomized clinical trial with three arms, comparing the use of systemic minocycline to probiotic alone and the combination of both, showed that the group that received the combined treatment with antibiotic and probiotic showed statistically significant results in the total reduction of lesions compared to the other groups. Also, there was a reduction in adverse events resulting from the chronic use of antibiotics. These results suggest that probiotics can be considered a therapeutic option or adjuvant for acne, providing a synergistic anti-inflammatory effect with systemic antibiotics.[14]

Given the potential outcomes of probiotics in maintaining the balance of the skin microbiota, as well as in insulin/IGF-1 and FOX01 signaling, with consequent positive effects in the treatment of acne, especially when used as adjuvant therapy,[14,15] this clinical trial aims to evaluate the comparative efficacy of a regimen containing an oral probiotic (Lactobacillus acidophilus + Bifidobacterium lactis) and topical treatment with adapalene 0.1% and benzoyl peroxide 2.5% in patients with mild to moderate acne.

PATIENTS AND METHODS

Study participants

We recruited 400 participants aged between 12 and 35 years, of both sexes, diagnosed with acne grades II and III, with mixed or oily skin, and skin phototype between I and IV, according to the Fitzpatrick scale. We excluded pregnant, lactating, or intending to become pregnant during the study period patients, as well as individuals who received treatments with corticosteroids and antimicrobials 30 days before selection and those who received immunosuppressant 90 days before selection.

The study was conducted in Osasco (SP), Brazil, at Medcin Instituto da Pele Ltda., and the study period was from April 18, 2018, to April 7, 2021. The Research Ethics Committee from São Francisco University (SP) approved the study protocol on December 14, 2018. CAAE: 03728318.5.0000.5514. Opinion number: 3,083,043. All participants signed the Informed Consent Form (ICF), and the research was conducted by Good Clinical Practices and the 1996 Declaration of Helsinki. We recruited 400 participants aged between 12 and 35 years, of both sexes, diagnosed with acne grades II and III, with mixed or oily skin, and skin phototype between I and IV, according to the Fitzpatrick scale. We excluded pregnant, lactating, or intending to become pregnant during the study period patients, as well as individuals who received treatments with corticosteroids and antimicrobials 30 days before selection and those who received immunosuppressant 90 days before selection.

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Study design and treatment

It was a randomized, double-blind, two-arm, placebo-controlled trial. It aimed to assess the superiority of treatment with an oral probiotic composed of Lactobacillus acidophilus, Bifidobacterium lactis, vitamins and minerals - Exímia Probiac® (EP) - combined with the association of topical adapalene 0.1% and benzoyl peroxide 2.5% - Epiduo® (PBA) - compared to the use of PBA associated with placebo in improving the clinical condition of patients with acne.

Eligible participants were randomized into two equal groups to receive one of the treatments. Topical and oral treatments were administered once daily. Patients were also instructed to use SPF 50 sunscreen daily. Everyone received a bottle on the first visit. The company FARMOQUÍMICA SA provided all study samples.

The study was divided into two phases of 90 days each, totaling 180 days. We assessed patients at the initial visit (D0) and then every 30 days, totaling seven visits. On visit D0, patients received randomized treatments and directions for use. In the first phase (90 days), patients received treatment with PBA associated with PE (investigational treatment - IT) or PE associated with placebo (comparator treatment - CT). In the second phase (90 days), patients received only oral treatment with EP or placebo. Figure 1 describes the study design.

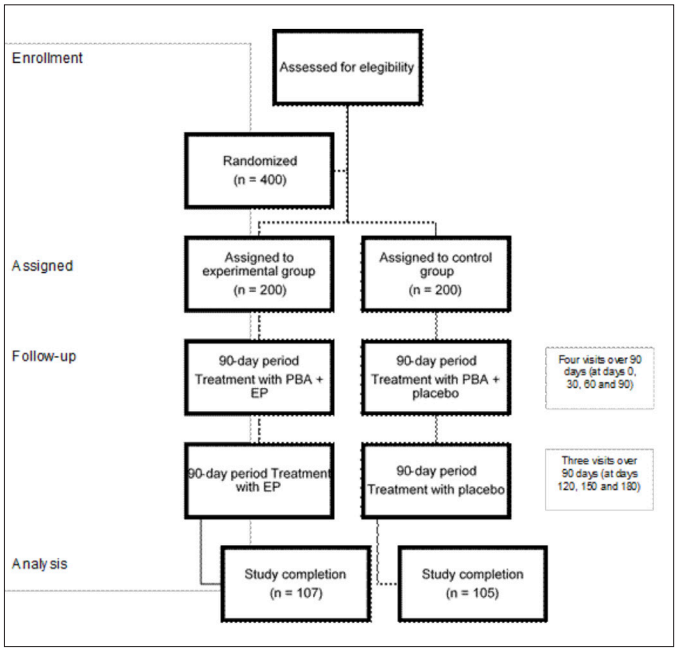

Figure 1: Study design

At each visit (D0, D30, D60, D90, D120, D150, and D180), we clinically evaluated the patients and recorded the results against the Investigator Global Assessment (IGA) scale.

Efficacy criteria

The primary variables of the study were the reduction of the IGA score to grade 1 or 0, as well as the reduction in the total number of inflammatory and non-inflammatory lesions in the facial region. We considered evaluations according to an established scoring scale to quantify IGA:

0 = Clean skin: residual hyperpigmentation and erythema may be present;

1 = Almost clear: some scattered comedones and a few small papules;

2 = Mild: less than half of the face affected, some comedones and some papules and pustules;

3 = Moderate: more than half of the face affected, some comedones, papules, and pustules. A nodule may be present;

4 = Severe: The entire face is severely affected by comedones, numerous papules and pustules, and some nodules and cysts.

Statistical analysis

We compared the results obtained from clinical, instrumental, and subjective evaluations between experimental times and, subsequently, between treatments. The hypothesis tests used in the study had a significance level of 95%, and the statistical power of these tests was above 80%. We conducted descriptive analyses of the variables studied using frequency tables and descriptive statistics. The percentage of participants with a reduction in the total number of inflammatory and non-inflammatory lesions and with regression of the IGA scale to no lesions (score 0) or almost no lesions (score 1) were evaluated using the z-test for comparison of two proportions.

Results were considered statistically significant at a significance level of 5% ($p \leq 0.05$). The significance level was controlled by rejecting the null hypotheses if the p-value was less than or equal to 5%.

RESULTS

Baseline clinical features

We selected 400 patients. A total of 146 participants were considered lost to follow-up; 34 were excluded due to low adherence; and eight were discontinued due to adverse events. Thus, 212 patients completed the study, 107 in the test treatment group and 105 in the comparator treatment group. The age range of final participants ranged from 12 to 35 years old, with an average of 17 years old. Table 1 describes baseline clinical characteristics. The distribution of patients was homogeneous in both groups.

Table 1: Baseline clinical characteristics of patients in both groups			
Parameter	**IT**	**CT**	**p-value**
N	107	105	
Men (%)	38.3	39.1	0.913
Women (%)	61.7	60.9	
IGA			
Mean ±DP	2 (2 – 3)	3 (2 – 3)	0.1701
Total lesions			
Mean ±DP	67 (46 – 105)	72 (53 – 110)	0.1894
Inflammatory lesions			
Mean ±DP	14 (6 – 22)	18 (13 – 24)	0.0022
Non-inflammatory lesions			
Mean ±DP	52 (34 – 80)	55 (36 – 84)	0.6405

Efficacy

Reduction in the IGA scale to 0 or 1

We assessed the primary efficacy parameter, reduction of the IGA scale to 0 or 1, by comparing the proportions at each of the times, starting from D30. Table 2 shows the descriptive results of means and standard deviations of IGA in both groups. We analyzed the proportion of patients with IGA 1 or 0, concerning the total number of patients at that time point (Table 3), to compare the proportions at each time point from D30 onwards. The results indicate that there was a significant difference in the proportion of participants with IGA 0 or 1, with the IT group being superior to the CT group at all experimental times ($p<0.05$) (Tables 4 and 5).

Reduction in the number of inflammatory lesions

Table 6 depicts descriptive results regarding the number of inflammatory lesions for both groups. Table 7 shows the proportion of patients who showed a reduced count of inflammatory lesions between the determined time and time 0. There was no statistically significant difference ($p<0.05$) between the two groups at any experimental time. However, at all experimental times, the proportion of patients who showed a reduction in inflammatory lesions was higher in the IT group compared to the CT group, although without statistical significance.

Reduction in the number of non-inflammatory lesions

Table 8 depicts descriptive results regarding the number of non-inflammatory lesions for both groups. Table 9 shows the proportion of patients who showed a reduction in the count of non-inflammatory lesions between the determined time and time zero. There was no statistically significant difference ($p<0.05$) between the two groups at any experimental time. However, at all experimental times, the proportion of volunteers who showed a reduction in inflammatory lesions was higher in the investigational group compared to the comparator group. Nevertheless, without statistical significance.

Adverse events

In the group that received the investigational treatment, one patient had an adverse event that was possibly related, and seven patients had an adverse event that was unlikely to be related to the probiotic drug EP. These events were mild gastroin-

Table 2: Description of IGA results at all times			
Parameter	**IT**	**CT**	**p-value**
Baseline (Mean±DP)	2.5±0.50	2.5±0.50	
D30 (Mean±DP)	1.7±0.81	1.9±0.88	0.0445
D60 (Mean±DP)	1.4±0.78	1.7±0.78	0.0079
D90 (Mean±DP)	1.2±0.69	1.5±0.71	0.0016
D120 (Mean±DP)	1.2±0.65	1.5±0.72	0.0015
D150 (Mean±DP)	1.2±0.65	1.3±0.78	0.0027
D180 (Mean±DP)	1.1±0.68	1.4±0.72	0.0218

Table 3: IGA regression proportion (Prop) (0 or 1) comparing investigational treatment to comparator treatment						
Time	**Prop (IT)**	**n (IT)**	**Prop (CT)**	**n (CT)**	**z**	**p-value**
D30	0.467	107	0.352	105	1.7006	0.0445
D60	0.623	107	0.457	105	2.4118	0.0079
D90	0.738	107	0.544	105	2.9426	0.0016
D120	0.738	107	0.543	105	2.9671	0.0015
D150	0.785	107	0.61	105	2.7833	0.0027
D180	0.774	107	0.648	105	2.018	0.0218

Table 4 - Total number of lesions							
Time	**D0**	**D30**	**D60**	**D90**	**D120**	**D150**	**D180**
				IT			
N	107	107	107	107	107	107	107
Mean	76.2	37.7	26.6	21.1	25.7	27.8	25
Median	67	34	20	15	16	22	19
Standard deviation	40.29	25.77	20.33	18.10	29.05	27.56	24.90
				CT			
N	105	105	105	105	105	105	105
Mean	84.0	49.1	37.3	31.9	36.8	32.2	33
Median	72	34	31	24.5	31	27	24
Standard deviation	45	50.76	29.22	28.94	31.44	26.67	33.06

testinal symptoms such as nausea, stomach pain, and heartburn. In this same group, 73 patients had adverse events related to the topical PBA medication. Of these, one was categorized as product-related, 37 as probable, 30 as possible, and five as unlikely. These events were skin signs and symptoms, such as erythema, edema, itching, and burning at the application site. All patients recovered or remained stable.

The group that received the control treatment reported one adverse event possibly related and one adverse event unlikely related to the placebo treatment. In this group, 70 patients had adverse events related to the use of PBA. These events were skin signs and symptoms, such as erythema, edema, itching, and burning at the application site. Of these, 33 were categorized as probable, 29 as possible, and eight as unlikely concerning the investigational product. All patients recovered.

DISCUSSION

The data obtained in the present study demonstrate that the use of oral probiotics (Lactobacillus acidophilus and Bifidobacterium lactis) associated with the fixed combination of adapalene 0.1% and benzoyl peroxide 2.5% presents superior efficacy than the same topical product associated with placebo to treat mild to moderate acne. One of the primary efficacy parameters of the study was the reduction of the IGA scale score to 0 or 1. The scale in question has five categories, from 0 to 4, where 0 means total absence of lesions and 4 indicates the greatest severity of acne, with the patient's entire face severely affected by comedones, papules, pustules, and some nodules and cysts. At the first study visit, the mean IGA in both groups (IT and CT) was 2.5, with a standard deviation of 0.5. The first phase of the study lasted 90 days, with visits every 30 days. In all these visits, there was a superiority in the proportion of patients with IGA 0 or 1 in the group that received the investigational treatment concerning the comparator group ($p<0.05$). At the 90-day visit, the mean IGA in the group that received the investigational treatment was 1.2, with a standard deviation of 0.69. In the comparator group, the mean IGA was 1.5, with a standard deviation of 0.71 ($p<0.05$).

In the second phase of the study, which lasted 90 days, we suspended the topical treatment so that the test group continued to receive oral treatment with probiotics and the control group continued to receive a placebo. During this period, the IGA averages were lower in all evaluations (120, 150, and 180 days) for the group that received probiotic treatment, and, in the last visit, the value found for this group was 1.1, with a standard deviation of 0.68, compared to 1.4 in the control group, with a Standard deviation of 0.72 ($p<0.05$).

Table 5: IGA regression ratio (0 or 1) comparing IT and CT						
Time	**Prop (IT)**	**n (IT)**	**Prop (CT)**	**n (CT)**	**z**	**p-value**
D30	0.907	107	0.914	105	-0.1974	0.5782
D60	0.935	107	0.943	105	-0.2512	0.5992
D90	0.963	107	0.933	105	0.9776	0.1641
D120	0.916	107	0.905	105	0.2836	0.3884
D150	0.944	107	0.975	105	0.5896	0.2777
D180	0.944	107	0.943	105	0.0336	0.4866

Table 6 - Description of inflammatory lesions							
Time	**D0**	**D30**	**D60**	**D90**	**D120**	**D150**	**D180**
				IT			
N	107	107	107	107	107	107	107
Mean	15.4	8.2	7.5	5.7	6.1	6.3	6.1
Median	14	6	5	4	5	4	4
Standard deviation	11.36	8.1	7.74	6.28	6.29	7.73	6.69
				CT			
N	105	105	105	105	105	105	105
Mean	19.5	11.4	10	7.8	8.6	8.6	8.4
Median	18	9	7	6	6	7	7
Standard deviation	10.28	9.24	9.21	7.33	7.92	8.11	7.43

The data also revealed a tendency towards superior results in the group that received the investigational treatment concerning the reduction in the total number of lesions, inflammatory and non-inflammatory lesions, although without statistical significance.

The administration of EP treatment for 90 days proved to be safe in the studied population, with only one patient having an adverse event possibly related to the therapy and seven patients having adverse events that were unlikely related to the treatment. These events were mild gastrointestinal symptoms, such as nausea, stomach pain, and heartburn, and did not determine the discontinuation of patients from the study.

The set of data presented indicates that, under the circumstances and limitations defined in the present study, treatment with the probiotic EP associated with the topical medication, composed of adapalene 0.1% and benzoyl peroxide 2.5%, is more effective than that treatment consisting of adapalene 0.1% and benzoyl peroxide 2.5% alone in patients with mild to moderate acne, with few reported adverse events.

A recent article by Navarro-López et al. (2021)[16] reported a growing number of current studies relating intestinal and cutaneous dysbiosis with the pathophysiology of acne, as well as with other diseases, such as atopic dermatitis and psoriasis. Several studies provide evidence of the influence of probiotic treatments aimed at modulating the skin and intestinal microbiota in these diseases and the positive impact of orally administered probiotics on these dermatoses. Although clinical studies with probiotics to treat acne are still scarce in the literature, several current studies have demonstrated a decrease in the intestinal microbiota diversity in patients with acne.[17,18] Therefore, it is plausible to think that probiotics as adjuvant therapy have a relevant role in the treatment and prognosis of this disease.

In 2013, Jung et al. used a probiotic mixture with strains of *Lactobacillus acidophilus*, *Lactobacillus delbrueckii bulgaricus*, and *Bifidobacterium bifidum* in 45 adults with acne. There was a 67% reduction in lesion counts at 12 weeks of treatment and an 82% reduction when the probiotic mixture was combined with oral minocycline.[14] These data are consistent with those found in this study, although there was no oral antibiotic treatment. If we consider the 90-day visit our study had a 72% reduction in the number of lesions in the group that received investigational treatment.

In a 2021 clinical study, Kim et al. demonstrated a 33.2% decrease in the total lesion count after 12 weeks of treat-

Table 7: Proportion of reductions						
Time	**Prop (IT)**	**n (IT)**	**Prop (CT)**	**n (CT)**	**z**	**p-value**
D30	0.757	107	0.848	105	-1.6549	0.9510
D60	0.794	107	0.838	105	-0.8211	0.7942
D90	0.785	107	0.923	105	-2.8314	0.9977
D120	0.794	107	0.857	105	-1.2035	0.8856
D150	0.794	107	0.914	105	-2.4702	0.9932
D180	0.841	107	0.886	105	-09447	0.8276

Table 8: Description of non-inflammatory lesions							
Time	**D0**	**D30**	**D60**	**D90**	**D120**	**D150**	**D180**
				IT			
N	107	107	107	107	107	107	107
Mean	608	29.5	19.1	15.4	19.7	21.4	18.9
Median	52	26	14	11	12	16	13
Standard deviation	36.73	22.2	16.3	15.48	26.55	23.90	21.51
				CT			
N	105	105	105	105	105	105	105
Mean	64.4	37.6	27.3	24.1	28.1	23.7	24.6
Median	55	26	22	15	22	20	15
Standard deviation	42.14	46.84	23.68	24.80	26.89	22.1	29.20

Table 9 - Proportion of reductions						
Time	**Prop (IT)**	**n (IT)**	**Prop (CT)**	**n (CT)**	**z**	**p-value**
D30	0.879	107	0.857	105	0.4593	0.323
D60	0.925	107	0.905	105	0.5347	0.2964
D90	0.953	107	0.904	105	1.3968	0.0812
D120	0.925	107	0.976	105	1.1951	0.116
D150	0.935	107	0.895	105	1.0275	0.1521
D180	0.935	107	0.924	105	0.3058	0.3799

ment with *Lactobacillus bulgaricus* and *Streptococcus thermophiles*.[19] Fabbrocini et al. found similar results in a study analyzing the effect of administering *Lactobacillus rhamnosus* to a group of 20 individuals with acne for 12 weeks, obtaining a 32% reduction ($p<0.001$) on a 5-point scale.

Although these studies used only probiotics in the evaluation, the results corroborate those found in this study. While the comparison between groups was not statistically significant in terms of lesion count, there was a significant reduction in the number of lesions. At the first visit, the average number of total lesions in the IT group was 76.2, with a standard deviation of 40.29, and, at the 180-day visit, this average was reduced to 25, with a standard deviation of 24.9.

Currently, there is a need for alternatives to the use of oral antibiotics for the treatment of acne. We know that these medications are associated with risks, especially when taken for a long time, such as opportunistic infections, gastrointestinal inflammatory processes, and the development of bacterial resistance.[20] Their prescription is justified by their anti-inflammatory action and not by their antibacterial activity.[21] Therefore, oral

probiotics, due to their immunomodulatory properties and lower potential to cause side effects, find a real possibility, when associated with other classic alternatives, to enhance the treatment of acne.

It is the first clinical trial to compare the use of oral probiotics associated with topical treatment in Brazilian patients. In this clinical trial, the treatment period was 180 days, a relatively long period compared to several similar clinical trials. The sample size was sufficient for the robustness of the data found. The study methodology, as well as the efficacy parameters such as the IGA scale and the reduction in the number of lesions, provided an absolute quantitative measure of improvement, and other clinical trials have used these same endpoints.[22] Blinding of the raters that generate these results for treatment allocations also allowed us to avoid the evaluation bias. New studies need to quantitatively and qualitatively assess the skin and gut microbiome before and after treatment, as well as the primary mediators and proteins involved, such as substance P, IGF-1 expression, insulin, and interleukin,[17] among others.

CONCLUSION

Exímia Probiac® associated with the Epiduo® product showed superior efficacy than treatment with Epiduo® associated with placebo in reducing the IGA scale in patients with mild to moderate acne, with statistical significance, and in reducing the number of lesions (inflammatory and non-inflammatory), without statistical significance. The test treatment was safe and well tolerated. The evidence on efficacy and safety shows that Exímia Probiac® should be considered in adjuvant therapy for acne control.

Observation: this was a sponsored study.

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