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Efficacy of BPO 2.5% Gel in the Acute and Maintenance Periods for Moderate or Severe Facial Acne Vulgaris

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Abstract

Background and objective: There is no evidence of efficacy for concomitant use of benzoyl peroxide (BPO) gel, adapalene gel, and antimicrobial agents for external treatment of the inflammatory phase of acne vulgaris, and there is little evidence for the utility of BPO gel for the maintenance phase after remission of inflammatory acne. Therefore, we investigated the effect of concomitant use of BPO gel, adapalene gel, and an antimicrobial agent for topical use for inflammatory-phase acne vulgaris and the efficacy of BPO gel for the maintenance phase.

Design and methods: The subjects were patients with moderate to severe acne vulgaris (6 to 30 inflammatory skin eruptions on one side of the face). A randomized 3 group parallel comparison study of inflammatory-phase treatment (step 1) was performed, followed by a randomized 2 group parallel comparison study of maintenance-phase treatment (step 2).

Results: In the inflammatory phase, both inflammatory and non-inflammatory skin eruptions were improved by concomitant use of BPO 2.5% gel+clindamycin 1%, concomitant use of BPO gel 2.5%+adapalene gel 0.1% and concomitant use of adapalene gel 0.1%+clindamycin 1%, respectively. For the maintenance phase, both adapalene 0.1% gel and BPO 2.5% gel were effective.

Conclusion: These results confirm that concomitant treatment with BPO gel, adapalene gel, and an antimicrobial agent for topical use is useful for the inflammatory phase of severe facial acne vulgaris, and that treatment with BPO 2.5% gel alone is useful for the maintenance phase in Japanese acne patients.

Keywords: Stratified randomized allocation; Open multicenter clinical study; Antibiotics; Benzoyl peroxide; Adapalene; Acne vulgaris

Introduction

Acne vulgaris develops in hair follicles and the sebaceous gland unit as comedones as the initial symptom. The condition is a chronic inflammatory disease caused by dyskeratosis of the hair follicle infundibular canal, accumulation of sebum in hair follicles, and inflammation induced by growth of *Propionibacterium acnes* (*P. acnes*) [1]. The guidelines for acne vulgaris treatment established by the Japanese Dermatological Association [2] recommend a combination of antibiotics and adapalene for treatment of the inflammatory phase, in which inflammatory eruption is the main symptom and adapalene for treatment of comedones in the maintenance phase after remission of skin lesions. However, treatment with antibiotics is often continued for a prolonged period against a small number of residual or recurrent inflammatory ruptions in the maintenance phase, and an increase in drug-resistant bacterial strains is of great concern. In other countries, including western countries, benzoyl peroxide (BPO)-containing formulations are recommended in guidelines because of concern about these resistances.

With this background, BPO formulations were approved as drugs for acne vulgaris in 2014 in Japan. BPO has antibacterial action against *P. acnes* and also promotes exfoliation of the stratum corneum, with effects on both inflammatory eruptions and comedones [3]. In the inflammatory phase, it is important to obtain a treatment effect as quickly as possible from the viewpoint of adherence, and a combination of adapalene formulations with antibiotics or BPO is recommended in the Global Alliance Acne Treatment Algorithm [4]. In Japan, the combined effect of adapalene gel and antibiotics for topical use is higher than those of the individual drugs, and quick improvement by this combination has been confirmed [5]. However, there is no evidence for a combination of BPO gel and adapalene gel or BPO gel and topical antibiotics. Moreover, although adapalene gel and BPO gel are standard treatment for the maintenance phase after remission, there is little evidence for the usefulness of BPO gel in the maintenance phase. In this study, we investigated the combined effect of BPO gel with adapalene gel or topical antibiotics in the inflammatory phase of acne vulgaris and the usefulness of BPO gel in the maintenance phase.

Methods

This study was performed after approval by the Institutional Review Board of Asai Dermatology Clinic (IRB number: 15000181, first approval on October 20, 2015). The protocol followed the Ethical Guidelines for Medical and Health Research Involving Human

Subjects (Ministry of Education, Culture, Sports, Science and Technology/Ministry of Health, Labour and Welfare Notification No. 3 of 2014), in conformity with the Declaration of Helsinki and was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN study ID: UMIN000019639). The study was performed by dermatologists at 32 medical institutions between November 2015 and March 2017. The institutions and investigators are shown in Table 1.

S. No.	Medical Institutions	Investigators
1	Kura Dermatology and Plastic Surgery	Ataru Matsukawa*
2	Chitofuna Dermatology Clinic	Toshiya Ebata*
3	Kitahara Dermatology Clinic	Hiroto Kitahara*
4	Shinjuku Minamiguchi Dermatology Skin Clinic	Toshitatsu Nogita*
5	Murahasi Clinic	Mariko Oe *
6	Miyabayashi Clinic	Rika Kikuchi*
7	Ogikubo Ueda Clinic	Shu Ueda*
8	Dobashi Dermatology Clinic	Eiji Dobashi*
9	Nomura Dermatology Clinic	Yuko Nomura*
10	Emiko Dermatology Clinic	Emiko Sawamura*
11	Tsukuda River-City Dermatology Clinic	Katsumi Tanito*
12	Pansy Skin Clinic	Hisae Mukaikubo*
13	Fukuda Skin Clinic	Hiromi Fukuda*
14	Mita Hifuka	Hiroki Kanda*
15	Iderea Clinic Daikanyama	Mami Chiba*
16	Akihabara Skin Clinic	Yuki Horiuchi*
17	Meiwa Hospital	Ichiro Kurokawa*
18	Tanioka Dermatology Clinic	Miki Tanioka*
19	Chitose Dermatology Plastic Surgery Clinic	Jun Mayama*
20	Fukuzimi Dermatology Clinic	Hidemi Yasuda*
21	Asai Dermatology Clinic	Toshiya Asai*
22	Kobayashi Dermatological Clinic	Masako Watanabe*, Noriko Yoshimura
23	Hiramoto Skin Clinic	Takeaki Hiramoto*
24	Hohki Dermatology Clinic	Ken Hohki*
25	Kobayashi Skin Clinic	Hitoshi Kobayashi*, Ken Arita
26	Yotsuya Sanchome Hifuka	Mina Yamada*
27	Queen's Square Medical Facilities	Tokuya Omi*
28	Yokohama Bashamichi Skin and Pain Clinic	Rika Hayashi*
29	Ruka Hifuka Clinic	Miki Seino*
30	Hukuro Dermatology Clinic	Shuhei Hukuro*
31	Noah Hifuka Clinic	Nanako Niiyama*, Fumiki Yamashita
32	Hiruma Dermatology and Otorhinolaryngology Clinic	Masatato Hiruma*
*: Investigator		

Table 1: Medical institutions.

Subjects and inclusion and exclusion criteria

In the first stage (inflammatory phase), the subjects were aged ≥ 16 years and met the inclusion criteria and did not meet the any exclusion criteria shown in Table 2a. In the second stage (maintenance phase), the subjects were those in whom remission of symptoms occurred in the first stage to a grade less than mild (≤ 5 inflammatory eruptions on the entire face with ≤ 3 on one side of the face) and met the all inclusion criteria shown in Table 2b.

Inclusion criteria (inflammatory phase)
Patients who met all of the following conditions were selected as subjects:
1) Moderate to severe acne vulgaris (6-30 inflammatory eruptions on one side of the face)
2) Written consent provided after receiving an explanation of the study content
3) Age ≥ 16 years at the time of obtaining consent. For patients <20 years old, consent was also obtained from a legal representative (such as the patient's parents)
Exclusion criteria
Patients who met one or more of the conditions below were excluded:
1) Treated for acne vulgaris within one month before the study
2) Contraindicated for the investigational drugs
3) Continuous use of non-steroidal anti-inflammatory drugs
4) Pregnant or possibly pregnant women, lactating women, and women who wanted to become pregnant during the study period

5) Judged as ineligible by the physician directing the study
6) Participation in another clinical study or post-marketing surveillance of other drugs for acne vulgaris within six months before the study

Table 2a: Inclusion and exclusion criteria in the first stage.

Inclusion criteria (maintenance phase)
Patients who met all of the following conditions were selected as subjects:
1) Reduction of inflammatory eruptions to ≤ 5 or fewer on the entire face with ≤ 3 on one side of the face within 12 weeks after treatment initiation in the first stage (inflammatory phase
2) Written consent provided after a re-explanation of the study content of the maintenance phase
Exclusion criteria
Patients who met the condition below were excluded:
1) Judged as ineligible by the physician directing the study.

Table 2b: Inclusion and exclusion criteria in the second stage.

Investigational drugs

The investigational drugs were 2.5% benzoyl peroxide (BPO) gel, 0.1% adapalene gel and 1% clindamycin (CLDM) gel or 1% CLDM lotion. A multicenter clinical study was performed with an open and stratified randomized allocation design. The first stage (inflammatory phase) used a 3-group parallel comparison design using combination therapy: Group A: BPO+CLDM, Group B: BPO+adapalene and Group C: adapalene+CLDM. The second stage (maintenance phase) had a 2-group parallel comparison design using monotherapy: Group 2A: adapalene, Group 2B, BPO.

Subjects

This was an exploratory clinical study, and the target sample size in the first stage was set at 60 in each of the 3 groups (180 in total). For the second stage, the target was set at 50 in each group (100 in total). Randomized allocation of the investigational drugs to Groups A, B and C in the first stage was the adaptive randomization method by the minimization method that performed to prevent biases in the number of inflammatory eruptions, sex ratio, and age. The minimization method was used with the number of inflammatory eruptions (6-20 and 21-30 eruptions on one side of the face), sex (male, female) and age (< or ≥ 20 years) as adjustment factors. For allocation to Groups 2A and 2B in the second stage, to prevent biases in pre-treatment, sex ratio, and age, randomized allocation was also performed using the minimization method with pre-treatment (Groups A, B, C), sex (male, female) and age (< or ≥ 20 years old) as adjustment factors.

Study design

The study design is shown in Figure 1. In the first stage, patients who gave written consent were randomly allocated to Groups A, B and C and observed for 12 weeks. This stage was considered complete when the number of inflammatory eruptions decreased to ≤ 5 on the entire face with ≤ 3 on one side of the face. The patient was then shifted to the second stage provided that the inclusion criteria were met within 12 weeks. In the second stage, the patients were randomly allocated to Groups 2A and 2B and observed for 12 weeks. The appearance of new inflammatory eruptions during the observation period was judged as relapse. This was recorded and the second stage was completed.

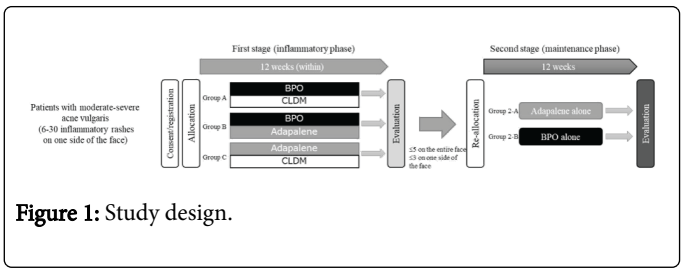

Figure 1: Study design.

Dosage and administration

Each drug was used following the dosage and administration specified in the package insert, with an appropriate amount of the drug applied to the affected region once a day (BPO and adapalene) or twice a day (CLDM). Throughout the study period, BPO gel was applied after washing the face in the morning (Group B) or before sleep (Groups 2A and 2B), adapalene gel was applied after washing the face before sleep and CLDM was applied after washing the face in the morning and before sleep.

Restriction of concomitant drugs and combination therapy

The following drugs and combination therapies were prohibited throughout the study period: drugs indicated for acne other than the investigational drugs; quasi-drugs and cosmetics with a preventive effect on acne; oral antibiotics (except for administration for ≤ 5 days against diseases such as a cold (when used, the name, dose, and duration of administration were recorded); chemical pealing, laser treatment and phototherapy of regions with acne, suction and pressing out of comedones; quasi-drugs and cosmetics with no history of use, except for moisturizing agents under the conditions stated below.

Routine cosmetics and moisturizing agents were permitted during the study. For patients who routinely used moisturizing agents, these were continued and their names and duration of use were recorded. For patients who did not usually use a moisturizing agent, use of an

agent was permitted as needed if skin symptoms such as scale/desquamation, skin irritation, and dryness developed during the study. The reason for use, name of the moisturizing agent, and duration of use were recorded.

Observation schedule and evaluation items

The observation schedule is shown in Table 3. For the subject background, the following items were surveyed at the time of registration: sex, birth date, age, duration of acne vulgaris, onset time, severity [6], presence of other allergic diseases, medical history, and complications that might influence evaluation of this study. For clinical symptoms, the numbers of inflammatory and non-inflammatory eruptions and total number (inflammatory+non-inflammatory) of eruptions were counted on the left and right sides and the entire face and recorded on each observation day.

	First stage (inflammatory phase)						Second stage (maintenance phase)						
	Week 0 Registration,allocation	Week 2	Week 4	Week 6	Week 8	Week 10	12 (Week 0), Re-registration, allocation	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
Hospital visit (observation)	•	•	•	•	•	•	•	•	•	•	•	•	•
Obtainment of consent, registration	•						•						
Subject background	•						•						
Observation of clinical symptoms	•	•	•	•	•	•	•	•	•	•	•	•	•
QOL (Skindex-16)	•						•						•
Confirmation of investigational drugs		•	•	•	•	•	•	•	•	•	•	•	•
Safety	<—												—>
*The trial shifted to the second stage (maintenance phase) when the number of inflammatory eruptions decreased to < 5 on the entire face with < 3 on one side of the face within 12 weeks in the first stage (inflammatory phase). The patients were re-registered and re-allocated													

Table 3: Evaluation schedule.

In the second stage (maintenance phase), the period of relief from symptoms was defined as the time to formation of one or more new inflammatory eruptions. QOL was evaluated using Skindex-16 (Japanese edition) [7], which were completed by the subjects. Daily records of topical use of the investigational drugs were kept by the subjects and confirmed by the physicians in charge, and adherence was evaluated and recorded as follows: 1: 100% adherence to drug application as instructed; 2: ≥ 75% to 100% adherence; 3: ≥ 50% to <75% adherence. 4: ≥ 25% to <50% adherence; and 5: <25% adherence.

Safety

Adverse events were defined as all undesirable and unintended signs, symptoms, and diseases that developed during the period from initiation of the first stage to completion of the second stage (discontinuation), regardless of the presence or absence of a causal relationship with the investigational drugs. When an adverse event was caused by an investigational drug, the symptom or disease, onset day, presence or absence of treatment and its content, outcome and judgment date, and association with the drug were described in the column for adverse events in the subject information record from.

Statistical analysis

All patients who participated in the study after giving consent were included in the analysis set. Patients whose symptoms could be evaluated were included in the efficacy analysis set. Patients with <75% adherence to drug application were excluded from the efficacy evaluation. For comparison among groups, the significance was set at a 2-sided level of 1.66% using Bonferroni correction in the first stage, in consideration of multiplicity of the test, and of 5% in the second stage. For within-group comparison, the significance was set at a 2-sided level of 5%. Analysis was performed using JMP Ver12.0 (SAS Institute).

The primary endpoint in the first stage (inflammatory phase) was the rate of reduction (%) of the number of inflammatory eruptions (between-group comparison using a Wilcoxon two-sample test). The secondary endpoints were the rate of reduction (%) of the number of non-inflammatory eruptions (Wilcoxon two-sample test); rate of reduction (%) of the total number of eruptions (Wilcoxon two-sample test), time required for reduction of the number of eruptions to ≤ 5 on the entire face with ≤ 3 on one side of the face (Kaplan-Meier method and log-rank test for between-group comparison); QOL using Skindex-16 (2-sample and one-sample t-tests for between-group and within-group comparisons, respectively, at weeks 0 and 12; and safety based on the incidence of adverse events and adverse effects (95% confidence interval (CI) calculated in each treatment group).

The primary endpoint in the second stage (maintenance phase) was the duration of symptom relief (Kaplan-Meier method and log-rank test for between-group comparison). The secondary endpoints were QOL by Skindex-16 and safety, which were both analysed as above.

Missing data in the first or second stage at week 12 (final observation day) were replaced by data for week 10, following the Last Observation Carried Forward (LOCF) concept. Similarly, missing data on each observation day (weeks 2, 4, 6, 8 and 10) were replaced by data collected at the nearest time point.

Study administration

This study was performed by the dermatologists at the medical institutions shown in Table 1 and led by the NPO Health Institute Skin Research Center (Chuo-ku, Tokyo). Secretariat work for conduct of the study was entrusted to EBC&M LLC (Minato-ku, Tokyo).

Results

Subject background

The background of the 158 registered patients is shown in Table 4. Thirty-six patients were male (Group A: 11, Group B: 11, Group C: 14) and 122 were female (Group A: 39, Group B: 40, Group C: 43). The mean age was 22.0 years for males and 23.9 years for females. The severity was moderate in 146 patients (Group A: 47, Group B: 48, Group C: 51) and severe in 12 (Group A: 3, Group B: 3, Group C: 6). The median numbers of eruptions were: inflammatory, 18 (Group A: 19.5, Group B: 17, Group C: 18); non-inflammatory, 23 (Group A: 21.5, Group B: 22, Group C: 30); and total, 48 (Group A: 45.5, Group B: 41.5, Group C: 52), with no significant difference among the groups.

		Allocation									Total		
		Group A			Group B			Group C					
		BPO+CLDM			BPO+Adapalene			Adapalene+CLDM					
		Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of patients		11	39	50	11	40	51	14	43	57	36	122	158
Age	Mean	21.3	24.1	23.5	22.1	24	23.6	22.4	23.6	23.3	22	23.9	23.5
	SD	4.5	6.5	6.2	5.7	5.4	5.5	7	4.8	5.4	5.9	5.6	5.7
Severity	Moderate	10	37	47	9	39	48	12	39	51	31	115	146
	Severe	1	2	3	2	1	3	2	4	6	5	7	12
Number of Eruption (median)	Inflammatory eruption	20	19	19.5	18	17	17	17	18	18	19	18	18
	Non-inflammatory	20	22	21.5	12	22	22	25	35	30	20	27	23
	All eruptions	42	48	45.5	44.5	41.5	41.5	44.5	57	52	44	49	48

Table 4: Background information for the subjects.

Disposition of the subjects (first stage)

The disposition of the subjects in the first stage is shown in Figure 2. The 158 patients who gave consent to participation in the study were randomly allocated to the three groups (Group A: 50, Group B: 51, Group C: 57) and included in the safety analysis set. After exclusion of 13 patients who discontinued, 8 who did not visit hospital after registration and 5 with <75% adherence to application of the investigational drugs, 132 patients (Group A: 43, Group B: 40, Group C: 49) were included in the efficacy analysis set. After excluding 9 dropout cases, 13 of 123 patients (Group A: 42, Group B: 37, Group C: 44) did not achieve the conditions required to move to the second stage. Excluding these patients, 110 patients (Group A: 38, Group B: 35, Group C: 37) participated in the second stage.

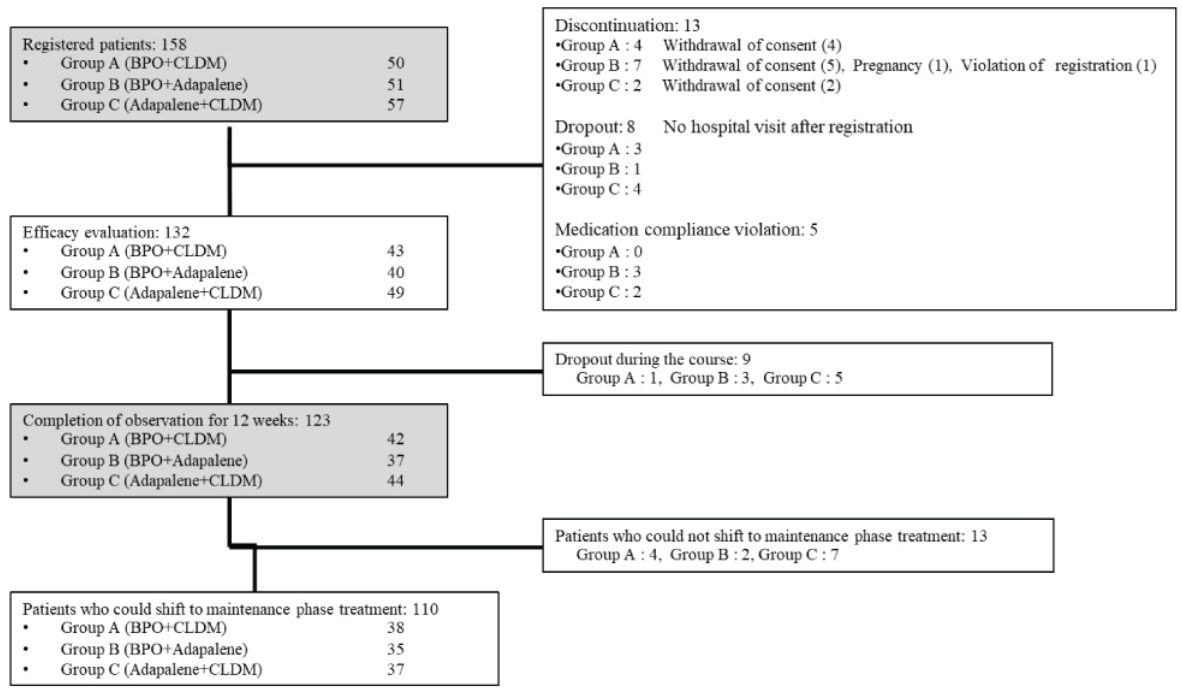

Figure 2: Disposition of subjects (first stage).

Reduction of inflammatory eruptions (first stage)

The median reduction rates of inflammatory eruptions at each time point relative to that at the time of registration are shown in Figure 3a. In all three groups, the number significantly decreased from week 2. The respective reduction rates in Groups A, B and C were 50.0%, 41.2% and 38.7% at week 2; 64.7%, 54.7% and 52.9% at week 4; 71.4%, 60.6% and 67.6% at week 6; 73.7%, 64.3% and 74.3% at week 8; 75.0%, 68.6% and 77.5%, at week 10; and 77.3%, 76.5% and 78.9% at week 12, showing decreases with time. The % reduction in Group A tended to be higher than that in Group C at weeks 2 ($p=0.0324$) and 4 ($p=0.0439$) and that in Group B at week 6 ($p=0.0219$), but there were no significant differences among the groups.

Reduction of non-inflammatory eruptions (first stage)

The median reduction rates of non-inflammatory eruptions at each time point relative to that at the time of registration are shown in Figure 3b. In all three groups, the number significantly decreased from week 2. The respective reduction rates in Groups A, B and C were 28.6%, 23.4% and 15.1% at week 2; 44.1%, 42.5% and 27.6% at week 4; 55.0%, 48.6% and 30.0% at week 6; 58.7%, 53.2% and 42.1%, at week 8; 62.9%, 54.2% and 42.5%, at week 10; and 65.0%, 59.0% and 45.2% at week 12, showing decreases with time. The reduction rates from weeks 2 to 8 were significantly higher in Group A than in Group C and tended to be higher in Group B than in Group C.

Reduction of the total number of eruptions (first stage)

The median reduction rates of the total number of eruptions at each time point relative to that at the time of registration are shown in Figure 3c. The number significantly decreased from week 2 in all three groups. The respective reduction rates in Groups A, B and C were 35.4%, 30.9% and 24.7% at week 2; 54.8%, 44.5% and 39.7% at week 4; 61.1%, 50.9% and 49.7% at week 6; 65.0%, 53.6% and 51.9% at week 8; 67.7%, 57.9% and 57.0% at week 10; and 70.0%, 62.6% and 58.4% at week 12, showing decreases with time. There were significant differences between Groups A and C at weeks 2 to 8.

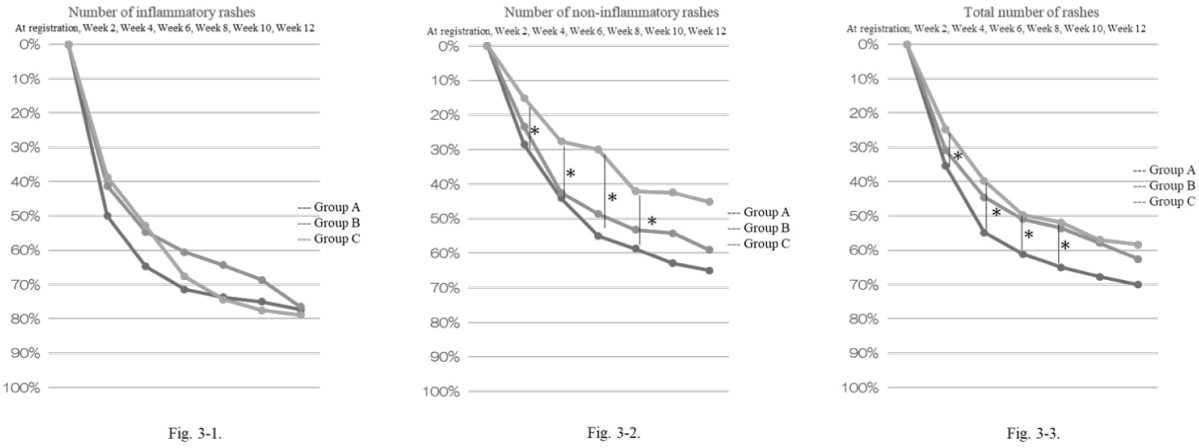

Fig. 3-1. Fig. 3-2. Fig. 3-3.

Figure 3: Rates of reduction of the number of eruptions relative to that at the time of registration (median).

Time required for reduction of the number of inflammatory eruptions (first stage)

The time required for reduction of the number of inflammatory eruptions to ≤ 5 on the entire face with ≤ 3 on one side of the face is shown as the time of shift to the second stage in Figure 4. A shift to the maintenance phase during the 12-week observation period occurred for 88.4, 87.5 and 75.5% of patients in Groups A, B and C, respectively. Kaplan-Meier analysis showed that the mean times to shift to the maintenance phase after treatment initiation were 7.4 ± 0.57, 7.5 ± 0.58 and 8.0 ± 0.53 weeks in Groups A, B and C, respectively, with no significant difference among the groups by log-rank test.

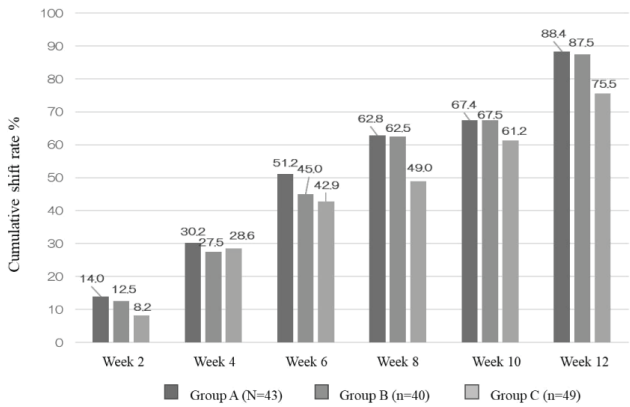

Figure 4: Cumulative rate of patients who shifted to the maintenance phase at each time point (weeks).

QOL using Skindex-16 (first stage)

The Skindex-16 scores at the time of registration and completion of the first stage are shown in Figure 5. In all groups, the feeling, function, and total scores significantly decreased, but there was no significant change in the symptom score in Group B or C. There was no significant difference in any of the scores at the time of registration or completion of the first stage among the groups.

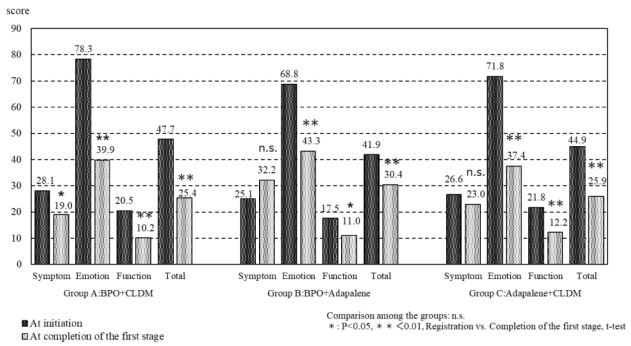

Figure 5: Changes in skindex-16.

Disposition of subjects (second stage)

The disposition of subjects in the second stage is shown in Figure 6. Of the 110 patients who shifted to the second stage, 108 gave re-consent and were randomly allocated to two groups (Groups 2A: 51, Group 2B: 57). Excluding 3 patients who withdrew re-consent and 7 who did not visit hospital after registration, 98 patients (Group 2A: 48, Group 2B: 50) were included in the efficacy analysis set. Excluding 6 patients who dropped out during the course, relief from symptoms was maintained for 12 weeks in 39 patients (Group 2A: 21, Group 2B: 18) and symptoms recurred or aggravated in 53 patients (Group 2A: 26, Group 2B: 27).

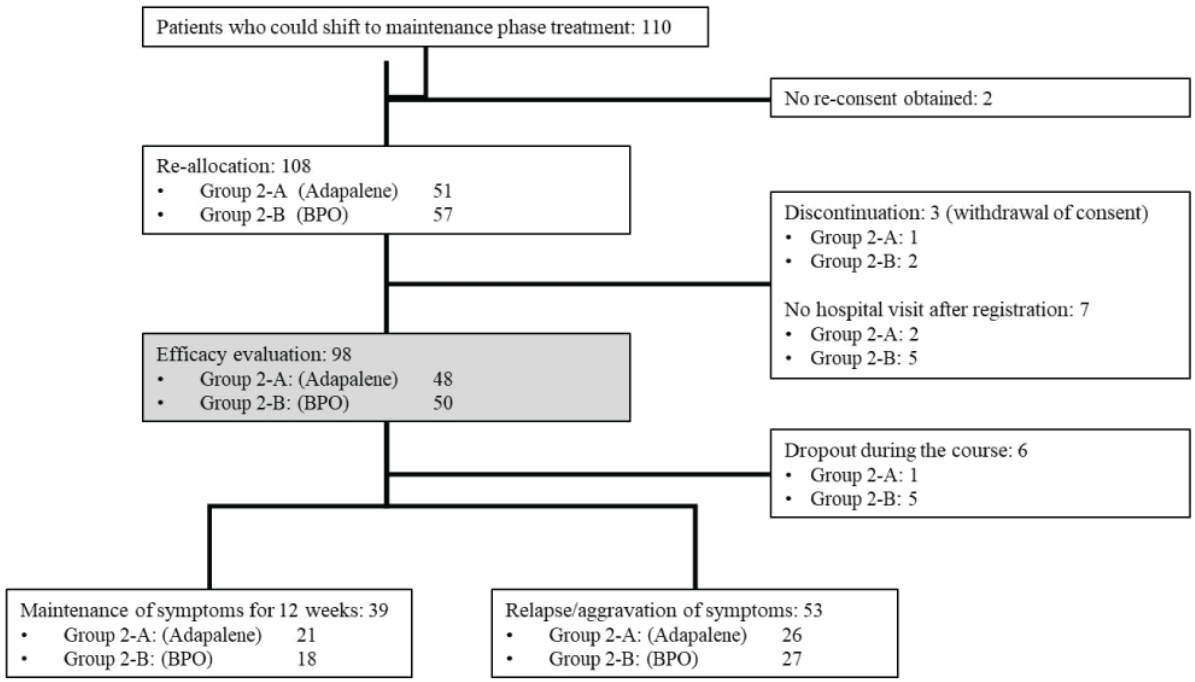

Figure 6: Disposition of subjects (second stage).

Duration of symptom relief (second stage)

Kaplan-Meier curves for symptom relief are shown in Figure 7. The mean durations were 9.1 ± 0.57 and 9.0 ± 0.54 weeks in Groups 2A and 2B, respectively, with no significant difference between the groups (log-rank test). The rates of maintenance of symptom relief throughout the 12-week observation period were 44.7% (21/47) and 40.0% (18/45) in Groups 2A and 2B, respectively, again with no significant difference between the two groups.

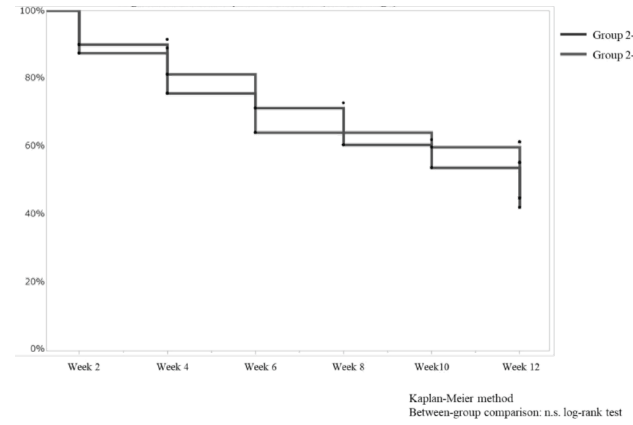

Figure 7: Maintenance phase treatment (second stage).

QOL using Skindex-16 (second stage)

Skindex-16 scores at the time of registration and completion of the first and second stages are shown in Figure 8. The symptom, feeling, function, and total scores were significantly decreased in Groups 2A and 2B at completion of the second stage. There was no significant difference in any score between Groups 2A and 2B at the time of registration or completion of the first or second stage.

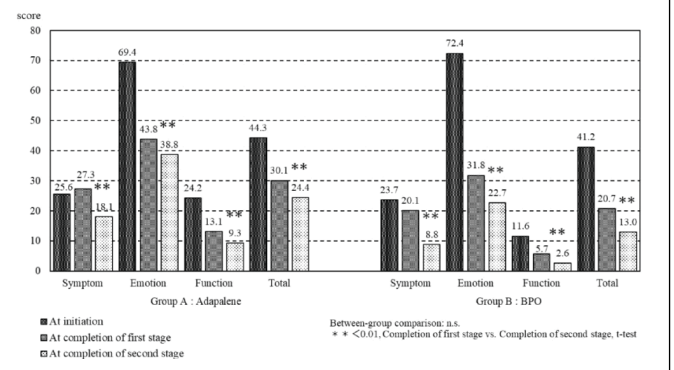

Figure 8: Changes in skindex-16.

Safety (first and second stages)

Adverse events observed in the first and second stages that were judged to have a causal relationship with an investigational drug are shown in Table 5. In the 158 patients included in the safety evaluation in the first stage, 27, 44 and 15 adverse effects (16, 30 and 10 patients)

occurred in Groups A, B and C, respectively. Many adverse effects developed early after treatment initiation. The trial was continued with additional moisturizing agent or without treatment of the adverse effect, and the symptoms resolved during the observation period (Table 5a). In the second stage, 108 patients were included in the safety evaluation, and 3 adverse effects (3 patients) developed in each of Groups 2A and 2B (Table 5b).

Group A					
Week 2	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**
Dryness (6) Irritation (3) Flare (3) Itch (2) Erythema (1) Contact dermatitis (1)	Irritation (2) Dryness (1) Erythema (1) Contact dermatitis (1)	Flare (1) Irritation (1)	Irritation (1)	Irritation (1)	Dryness (1) Itch (1)
16 cases/10 patients	5 cases/5 patients	2 cases/2 patients	1 case/1 patient	1 case/1 patient	2 cases/ 1 patient
Group B					
Week 2	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**
Irritation (13) Dryness (9) Erythema (3) Flare (2) Itch (1) Skin exfoliation (scale/ desquamation) (2) Asteatosis (1) Contact dermatitis (1)	Irritation (4) Dryness (2) Dermatitis (1)	Dryness (2) Flare (1) Itch (1)			Asteatotic eczema (1)
32 cases/20 patients	7 cases/7 patients	4 cases/3 patients	0 case/0 patient	0 case/0 patient	1 case/1 patient
Group C					
Week 2	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**
Irritation (2) Dryness (1) Erythema (1) Skin exfoliation (scale/ desquamation) (1) Asteatosis eczema (1)	Dryness (1) Erythema (1) Itch (1) Asteatosis eczema (1)	Contact dermatitis (1)	Irritation (1) Dryness (1)	Dryness (1)	Dryness (1)
6 cases/5 patients	4 cases/2 patients	1 case/1 patient	2 cases/2 patients	1 case/1 patient	1 case/1 patient

Table 5a: Development of adverse effects (first stage).

Group 2A					
Week 2	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**
Erythema (1)	Dryness (1)				Asteatotic eczema (1)
1 case/1 patient	1 case/1 patient	0 case/0 patient	0 case/0 patient	0 case/0 patient	1 case/1 patient
Group 2B					
Week 2	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**
	Dryness (1) Flare (1)		Flare (1)		
0 case/0 patient	2 cases/2 patients	0 case/0 patient	0 case/0 patient	1 case/1 patient	0 case/0 patient

Table 5b: Development of adverse effects (second stage).

Discussion and Conclusion

For inflammatory-phase acne vulgaris with inflammatory eruption, it is important to obtain a treatment effect as quickly as possible to promote adherence. A combination of adapalene with antibiotics or BPO is recommended by the Global Alliance Acne Treatment Algorithm [4]. In Japan, it has been shown that the combined effect of adapalene gel and antibiotics for topical use is higher than those of individual drugs and achieves rapid improvement. However, there is no evidence for the efficacy of a combination of BPO gel and adapalene gel or of BPO gel and topical antibiotics. Treatment with adapalene gel and BPO gel is standard for the maintenance phase after remission of inflammatory eruption, but there is little evidence for the utility of BPO gel in the maintenance phase. Thus, to investigate the combined effects of BPO gel with adapalene gel and with topical antibiotics for the inflammatory phase of acne vulgaris and the efficacy of BPO gel for the maintenance phase, a randomized 3-group parallel comparison study on inflammatory phase treatment (first stage) was performed, followed by a randomized 2-group parallel comparison study on treatment in the maintenance phase (second stage).

In the first stage (inflammatory phase), the numbers of inflammatory, non-inflammatory and total eruptions decreased in Group A (BPO gel 2.5%+CLDM 1%), Group B (BPO gel 2.5% +adapalene gel 0.1%) and Group C (adapalene gel 0.1%+CLDM 1%) and the effect of each combination therapy was equivalent to or higher than the effect in a previous study of a combination of 0.1% adapalene gel and 1% CLDM lotion performed in Japan, which was found to be satisfactory [8,9]. The number of inflammatory eruptions was markedly reduced by a compound formulation of 3% BPO and 1% CLDM early in the inflammatory phase, and a combination of these drugs showed a similar tendency [10,11]. In the shift of treatment to the maintenance phase after withdrawal of topical antibiotics, withdrawal of a single drug may be more acceptable than switching of a compounded formulation. Patients may better understand that treatment of the inflammatory phase is complete and that they are shifting to treatment for the maintenance phase. This possibility may require further investigation of adherence to acne treatment.

There were no significant differences in safety or QOL among the groups, but drug-associated skin symptoms, such as skin irritation, tended to be more frequent in Group B (adapalene+BPO). This was reflected in the slightly lower improvement of QOL in this group,

although the improvement was still significant compared with that at the time of registration. Similar skin symptoms, such as a feeling of irritation, were noted in patients treated with a compound formulation of 3% BPO and 1% CLDM and moisturizing agents to counter early skin irritation may be needed with this treatment.

In the second stage (maintenance phase), sufficient efficacy was observed in Group 2A (adapalene gel 0.1%) and Group 2B (BPO gel 2.5%) and no skin symptoms, such as dry skin, developed in patients who shifted from inflammatory to maintenance phase treatment, confirming the efficacy of both agents as drugs for the maintenance phase. Maintenance of the effect and the safety of adapalene gel and BPO gel have been demonstrated in one-year studies [9,12,13] and these were reconfirmed in the present study.

For the maintenance phase after remission of inflammatory eruption, withdrawal of topical antibiotics is recommended to avoid the issue of resistant bacteria. The present study confirmed the usefulness of monotherapy with 2.5% BPO gel for the maintenance phase. The results suggest that an appropriate and active approach to treatment of acne in the maintenance phase is required, with collection of evidence for target patient selection criteria for maintenance phase treatment with adapalene and BPO.

Conflict of Interest

Planning and conduct of this study were mainly performed by the NPO Health Institute Research of Skin (Chuo-ku, Tokyo), with funding provided by Maruho Co., Ltd.

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