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ORIGINAL ARTICLE

Clinical and bacteriological evaluation of adapalene 0.1% gel plus nadifloxacin 1% cream versus adapalene 0.1% gel in patients with acne vulgaris

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ABSTRACT

This multicenter, randomized parallel group study investigated the efficacy and tolerability of adapalene 0.1% gel plus nadifloxacin 1% cream (combination therapy) compared with adapalene gel (monotherapy) during 12-week treatment of acne vulgaris. A total of 184 Japanese patients aged above 12 years with moderate to severe acne as indicated by the Japanese severity grading criteria were randomized to combination therapy (*n* = 84) and monotherapy (*n* = 100) groups, both having comparable demographic and baseline characteristics. Adapalene was applied only to inflammatory acne lesions in order to minimize skin irritation and ensure the treatment results. Efficacy and safety evaluations, treatment compliance and satisfaction with drug application were periodically monitored. The combination therapy provided a significantly greater efficacy than adapalene in decrement of inflammatory papulopustular lesions at 4 weeks and thereafter (*P* = 0.0056). The overall judgment of the therapeutic efficacy by the physician at the end of study revealed a significant difference (*P* = 0.02496) between the groups in favor of combination therapy. Dryness was reported in a greater proportion of patients undergoing monotherapy than combination therapy at weeks 2 and 4 (*P* = 0.04652). The patient self-assessment in satisfaction with the drug application at the end of study revealed a significant difference (*P* = 0.00268) between the groups in favor of combination therapy. Among 76 strains of *Propionibacterium acnes* isolated from 87 patients, no strain was resistant to nadifloxacin. Thus, the simultaneous use of adapalene and nadifloxacin may provide an additive and complementary effect, resulting in clinical superiority and greater patient adherence compared to adapalene monotherapy.

Key words: **acne vulgaris, adapalene, combination therapy, nadifloxacin, *Propionibacterium acnes*.**

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit with multifactorial pathogenesis, affecting nearly every teenager at some stage, and often persisting into adulthood.[1] Androgen-induced increase in sebum production, altered keratinization, release of inflammatory mediators and bacterial colonization of hair follicles by *Propionibacterium acnes* are primary pathogenic features. Family history and diet may also have important roles in the disease.[2] Acne can cause not only permanent disfigurement but also significant psychological morbidity unless appropriately treated.[3] Therefore, each patient needs a suitable regimen for clearing lesions that provides satisfactory treatment results. Reflecting the complex and multifactorial contributors to acne pathogenesis, the available treatments consist of topical retinoids as first-line therapy for mild acne, topical retinoids in combination with antibiotics for moderate acne and isotretinoin for severe nodular acne.[4–6]

Adapalene is a third-generation topical retinoid primarily used in the treatment of mild to severe acne.[7,8] A good number of studies have shown the benefit of combining adapalene with topical acne medications.[9–12] The Japanese Dermatological Association-initiated guideline for the treatment of moderate to severe acne vulgaris also strongly recommends adapalene either alone or in combination with topical antibiotics such as nadifloxacin.[13] Nadifloxacin is a potent, broad-spectrum, quinolone agent approved for topical use in acne vulgaris and skin infections in Japan and European countries.[14] Kobayashi *et al.*[15] reported that the combination of topical adapalene and nadifloxacin is superior to adapalene monotherapy in reducing the number of lesions and occurrence of side-effects in the treatment of inflammatory acne. In the present randomized

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multicenter trial, we extended their study to confirm efficacy and safety of the adapalene and nadifloxacin combination in comparison to adapalene alone. We also examined antimicrobial susceptibility of *P. acnes* isolated from the lesions to nadifloxacin to clarify the prevalence of antibiotic-resistant strains among the enrolled patients.

METHODS

All study procedures were reviewed and approved by institutional review boards, and Good Clinical Practice and the principles of the Declaration of Helsinki were followed. All patients provided written informed consent before entering the study. If the patients were under the age of 18 years, the informed consent was obtained from parents or legal guardians.

Study population

Male and female patients aged at least 12 years with moderate to severe acne vulgaris were enrolled. Patients with moderate acne had 6–20 inflammatory lesions, and those with severe acne had 21–50 on a half side of the face, as indicated by the Japanese grading criteria for acne severity.[16] Patients taking certain topical and systemic treatments such as antibiotics, retinoids and contraceptives were required to undergo specified washout periods before they could enter the study. Subjects were excluded from the study if they had acne conglobata, acne fulminans, acne secondary to medication, occupational acne or other dermatological conditions requiring systemic therapy. Women were excluded if they were pregnant, planning to be pregnant or lactating. Men with beards were excluded if these were likely to cause interference with study assessments.

Study design

This was a 12-week, multicenter, randomized parallel group study examining the efficacy and safety of adapalene plus nadifloxacin relative to adapalene alone during 12-week treatment of acne vulgaris. The study was undertaken in collaboration with the Acne Study Group consisting of 41 investigators (see the list of the contributors at the end of manuscript) in Japan between April 2010 and March 2012. Eligible subjects were allocated into adapalene plus nadifloxacin treatment (combination therapy) and adapalene treatment (monotherapy) groups using enveloped lots picked out before the treatment. All patients were instructed to treat the inflammatory acne lesions with adapalene 0.1% gel once daily at night after washing and moistening the facial skin. In the combination therapy group, patients received nadifloxacin 1% cream in the acne lesions twice daily in the morning and immediately after application of adapalene gel at night. Adapalene was applied only to inflammatory acne lesions in order to minimize skin irritation and ensure the treatment results. Both drugs were applied as a thin layer to the inflammatory acne lesions. Following randomization at the first visit, patients had baseline assessments necessary for the study. Patients attended the clinic at weeks 2, 4, 8 and 12 of treatment for monitoring efficacy and safety evaluations as well as the treatment compliance and satisfaction with the drug application. Patients could withdraw from the study at any time. Where possible, patients who did not complete the study were to be fully evaluated.

Efficacy assessment

The investigators counted the number of inflammatory acne lesions (papules and pustules) on each half of the face at each follow-up visit. The overall judgment of therapeutic efficacy by the physicians at the end of study was made according to the following scale: excellent (>75% reduction), good (50–75% reduction), fair (25–50% reduction) and bad (<25% reduction or increased number of lesions).

Safety assessments

In comparison of facial tolerability at baseline and at each follow-up visit, the investigators questioned the patients to elicit adverse dermatological as well as non-dermatological events that were not present when treatment started or pre-existing local conditions that became more severe during the application period. Patients assessed burning and dryness, which were the most frequently observed skin signs, on a 4-point scale ranging from none, mild, moderate to severe at each follow-up visit.

Satisfaction assessment

Patients assessed satisfaction with the drug application rating on a 5-point scale, ranging from very satisfied, satisfied, fair, unsatisfied to very unsatisfied at completion of the study.

Microbiological analysis

At the entry, samples were obtained from the acne lesions of patients who gave permission for bacteriological studies by the method of Ross *et al.*[17] The bacteriological examination was performed by the method of Ishida *et al.*[18] Susceptibility of the isolated bacteria to nadifloxacin (Wako, Tokyo, Japan) was determined by measurement of minimum inhibitory concentration (MIC) using the agar dilution method according to the guidelines of the Clinical and Laboratory Standards Institute.[19]

Statistical analyses

Therapeutic effect was obtained based on the changes from baseline in number of lesions between groups for all follow-up time points. Missing values were inputted for the analysis using the last observation carried forward method. *P*-values were obtained using Wilcoxon rank sum test. Comparison of the overall judgment of therapeutic efficacy and the safety evaluation was conducted using Fisher's exact test. Results were considered significantly different if $P < 0.05$.

RESULTS

Disposition of patients

A total of 188 patients participated in the study and randomly assigned to the group treated with adapalene plus nadifloxacin ($n = 87$) and with adapalene ($n = 101$) (Table 1). A total of 184 patients (97.9%) completed the study. Reason for withdrawing

Table 1. Summary of patient disposition

	Adapalene plus nadifloxacin (n = 87)	Adapalene (n = 101)
Patients completing study	84	100
Patients discontinuing study	3	1
Adverse event	1	0
Lost to follow up	2	1

from the study included an adverse event (one patient) and lost to follow up (three patients).

Patient demography and baseline characteristics

Demographic data are shown in Table 2. All patients were Japanese, consisting of more females than males. The average age was similar between the two groups, ranging 12–53 years. Mean inflammatory lesion counts at baseline were 13.1 and 11.4 in the combination therapy and monotherapy groups, respectively, with no statistical difference. The ratio of severe to moderate acne was higher in the combination therapy group than the monotherapy group. Thus, the treatment groups were balanced for the demographic and baseline characteristics.

Efficacy evaluation

Mean percentage change in the inflammatory lesion count from baseline at weeks 2, 4, 8 and 12 are shown in Figure 1. Both combination therapy and monotherapy groups indicated a significant percent reduction of inflammatory lesions at week 2 compared to the baseline. There was a significantly greater reduction with combination therapy (45%) than with monotherapy (24%) ($P < 0.0001$ vs monotherapy) at week 4. This tendency held true at 8 weeks (combination therapy, 54%; monotherapy, 39%; $P = 0.0035$ vs monotherapy) and 12 weeks (combination therapy, 66%; monotherapy, 51%; $P = 0.0056$ vs monotherapy). The treatment compliance was comparable between the two groups, because mean drug application days per week were more than six throughout the study in both groups. The overall evaluation of the therapeutic

Table 2. Baseline characteristics of the patients

Characteristic	Adapalene plus nadifloxacin (n = 87)	Adapalene (n = 101)
Age, years		
Mean (range)	23.3 (12–53)	22 (12–40)
Range	12–53	12–40
Sex, n (%)		
Female	63 (72.4)	62 (61.4)
Male	22 (27.6)	38 (38.6)
Inflammatory lesion counts		
Mean (SD)	13.1 (7.06)	11.4 (4.55)
Severity, half face		
Moderate	77	97
Severe	10	4

SD, standard deviation.

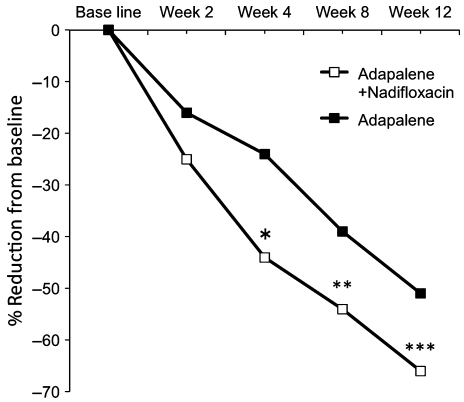

Figure 1. Mean percentage reduction in inflammatory lesion counts from 0–12 weeks (last observation carried forward) after treatment with adapalene plus nadifloxacin and adapalene. *$P < 0.0001$, **$P = 0.0035$, ***$P = 0.0056$ (vs) adapalene.

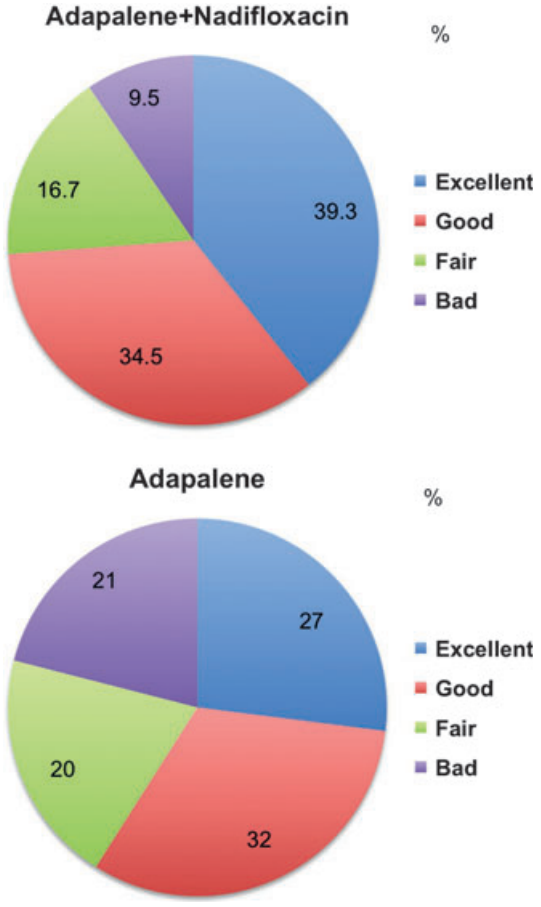

Figure 2. Overall evaluation of the therapeutic effect at the end of study as judged on a 4-point scale ranging from excellent to bad. *$P = 0.02496$ (vs) adapalene.

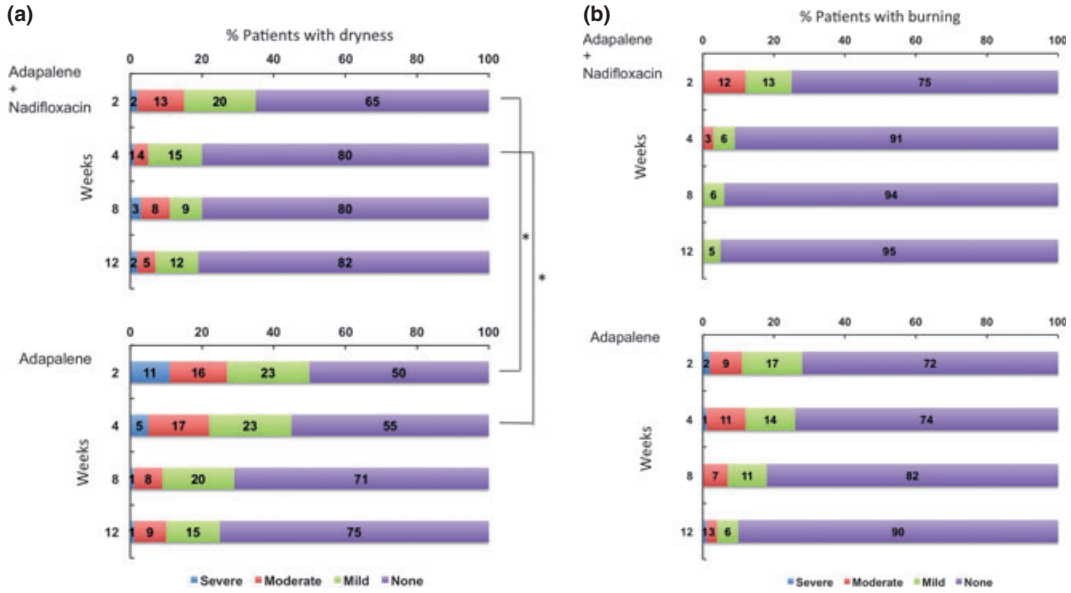

Figure 3. Investigator's assessment in dryness (a) and burning (b), rating on a 4-point scale ranging from none to severe during treatment with adapalene plus nadifloxacin and adapalene. *P = 0.04652 (vs) adapalene.

effect at the end of study was judged as excellent or good in 62 (73.8%) patients receiving combination therapy and in 59 (59%) patients receiving monotherapy (Fig. 2). A significant difference (P = 0.02496) was found between the groups in favor of combination therapy.

Safety assessment

Dryness and burning were the most frequently experienced adverse local effects, and occurred in various proportions of the patients throughout the study. Thus, 35% and 50% of patients in the combination therapy and monotherapy groups, respectively, felt dryness at week 2 with a statistically significant difference (P = 0.04652) (Fig. 3a). The number of patients with this symptom was decreased thereafter, with statistically significantly fewer patients experiencing dryness in combination therapy than in monotherapy at week 4 (P = 0.04652). There was no significant difference in the severity of burning between the combination therapy group and the monotherapy group (Fig. 3b). Dryness and burning was mild in intensity in most patients while the number of patients with severe symptoms was minimal throughout the study period. One patient receiving combination therapy withdrew from the study because of severe skin irritation. No patients reported systemic adverse events.

Satisfaction assessment

The patients' self-assessment in satisfaction with the drug application at the end of study were very satisfied and satisfied in one (1.4%) and 27 (37%) patients, respectively, in the combination therapy group and in zero and 15 (17.4%) patients, respectively, in the monotherapy group (Fig. 4). A significant difference (P = 0.00268) was found between the groups in favor of combination therapy.

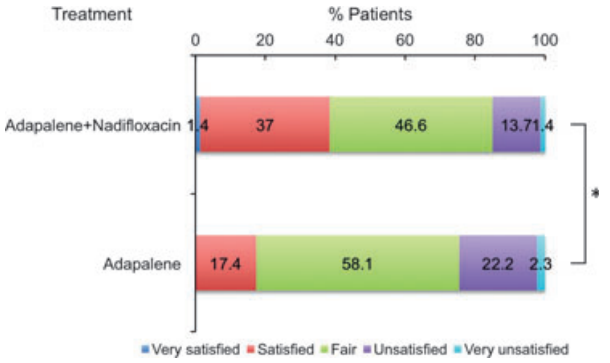

Figure 4. Patient self-assessment in overall satisfaction with the drug application, rating on a 5-point scale ranging from very satisfied to very unsatisfied at the end of study. *P = 0.00268 (vs) adapalene.

Bacteriological evaluations

Among 87 patients who gave permission for bacteriological studies, 76 strains of *P. acnes* were isolated. One strain of *P. acnes* had an MIC of nadifloxacin at 16 μg/mL while MIC against the rest strains ranged from less than 0.06–0.5 μg/mL. MIC50 and MIC90 of nadifloxacin against *P. acnes* were 0.25 and 0.5 μg/mL, respectively.

DISCUSSION

The present study showed that the combination of adapalene and nadifloxacin provided a significantly greater efficacy than adapalene in decrement of inflammatory lesions of moderate and severe acne vulgaris. The overall judgment of the therapeutic effect at the end of study revealed that the addition of

nadifloxacin to adapalene was more efficacious compared to adapalene alone. Adapalene and nadifloxacin are potent anti-acne drugs with different pharmacological activities. Thus, the simultaneous use of these topical preparations may provide additive and complementary effects, resulting in clinical superiority of the combination therapy to monotherapy.[20,21]

Tolerability is a critical factor in patient compliance with topical acne therapies. In the present study, both treatments were well tolerated and only one patient in the combination therapy group withdrew from the trial because of severe irritation. Reports of dryness were greater in patients receiving adapalene than those receiving adapalene plus nadifloxacin during the initial 4 weeks. On the other hand, comparable patients experienced burning between the combination therapy and monotherapy groups. While these side-effects are reported in various proportions of acne patients under treatment with either adapalene or nadifloxacin, the moisturizing effect of cream-based topical nadifloxacin may partly explain alleviation of dryness caused by adapalene.

The present bacterial examination revealed that no strain was resistant to nadifloxacin among 76 strains of *P. acnes* isolated from 87 patients. Over the past 20 years, concern has grown about the gradual worldwide increase in the prevalence of antibiotic-resistant *P. acne* strains due to extensive use of antibiotic therapy in the treatment of bacterial infection.[22] The emergence of antibiotic-resistant *P. acnes* may lead to therapeutic failure in acne vulgaris. In this European multicenter study, however, both nadifloxacin and erythromycin cream had similar clinical benefits, while the proportion of resistant *P. acnes* isolated from the erythromycin-treated group at the end of the trial was significantly increased compared to the nadifloxacin-treated group.[23] Thus, the association between the number of patients carrying antibiotic-resistant microorganisms and overall treatment results are not straightforward. We isolated a *P. acnes* strain with MIC of nadifloxacin at 16 μg/mL while the other strains had an MIC of less than 0.06–0.5 μg/mL, indicating rare presence of the strain with reduced susceptibility to nadifloxacin. It may be possible that local accumulation of nadifloxacin at high doses by skin application effectively kills *P. acnes*, even with the high MIC in acne treatment.

As teenagers gain independence during adolescence, their attitudes toward treatment and adherence to the prescribed regimen may be adversely affected. Parents and patients may not always be adequately educated about the causes and treatment of acne, which may further delay or affect successful treatment.[24,25] Poor adherence to therapy is a barrier to successful acne treatment. In fact, a study utilizing a simple validated questionnaire reveals the high rate of poor adherence in Japanese acne patients.[26] Factors with an impact on adherence include satisfaction with treatment and the experience of side-effects. Thus, we suggest that adapalene plus nadifloxacin is associated with greater patient adherence compared with adapalene monotherapy because of more efficacy and comparable or even lower incidence of the local side-effects. In addition, fast therapeutic results may reduce the risk of developing bacterial resistance.

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