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ORIGINAL ARTICLE

Efficacy of combined topical treatment of acne vulgaris with adapalene and nadifloxacin: A randomized study

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ABSTRACT

Topical retinoid and antibiotic combination therapy is an integral part of acne treatment and is considered the appropriate first-line therapy according to the Japanese guideline for moderate and severe acne. In this combination, clindamycin or doxycycline are mostly used as antibiotics, but there have been no reports on the effectiveness of nadifloxacin, a widely used antibiotic in Japan and European countries for acne, in combination with topical retinoid. To confirm the efficacy and safety of adapalene gel and nadifloxacin cream in the treatment of Japanese patients with acne vulgaris, a total of 50 patients were randomized to the two groups, the combination therapy and the adapalene monotherapy, and each therapy was tested for 8 weeks. The percentage reduction in the number of inflammatory acne lesions was evaluated and the safety was monitored through adverse events. The combination of adapalene gel and nadifloxacin cream produced a significantly higher reduction in the inflammatory lesions at 2 weeks ($P = 0.047$) and at 8 weeks ($P = 0.011$) after the starting than did adapalene gel monotherapy. The combination did not elevate the side effects of erythema and scale scores, but rather significantly depressed erythema at 1 week. This study showed the efficacy and safety of the combination therapy of nadifloxacin cream with adapalene gel for the inflammatory acne.

Key words: acne, adapalene, antibiotics, nadifloxacin, randomized study.

INTRODUCTION

A number of clinical trials for inflammatory acne have shown that combination therapy with a topical antibiotic and retinoid is more efficacious than monotherapy.[1,2] Previous studies of combination therapy were performed with tetracyclines, macrolides and benzoyl peroxide as antibiotics.[3–5] However, there have been no reports of clinical study using nadifloxacin (NDFX), which is a fluorinated quinolone derivative widely used in Japan and European countries as a topical antibiotic for the treatment of acne.[6–8] In addition to its therapeutic effectiveness, NDFX is considered to be beneficial because it does not generate resistant bacteria by virtue of its inhibitory action on DNA gyrase and topoisomerase IV interaction. In fact, no increase of NDFX-resistant *Propionibacterium acnes*, *Staphylococcus aureus* or *Staphylococcus epidermidis* was found in European studies.[9]

In this randomized study, we sought to investigate whether combination therapy with NDFX cream and adapalene gel is safe and superior to adapalene gel monotherapy for Japanese patients with acne.

METHODS

Patients and study design

The efficacy and safety of adapalene gel 0.1% (Differin gel 0.1%; Shionogi, Osaka, Japan, and Galderma Japan, Tokyo, Japan) and NDFX cream 1% (Acuatim cream 1%; Otsuka Pharmaceutical, Tokyo, Japan) were compared with adapalene gel alone in one general hospital (University of Occupational and Environmental Health Japan) and two private dermatology clinics (Dr T. Nakagawa and Dr K. Fukamachi) in January–December 2009. A total of 50 outpatients with moderate to severe acne were enrolled in this study. The severity was determined according to the Japanese acne grading system,[10] and the patients had 5–50 inflammatory lesions on the unilateral face. Patients or their parents (if the patients were below 20 years of age) provided informed consent. Any other treatments for acne, except for moisturizers and vitamin B2 and C supplements, were prohibited for at least 4 weeks before the beginning of the study. The patients agreed to not change their skin care during this trial. Individuals who were pregnant or had other skin diseases were excluded from

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this study. Patients were free to withdraw from the study at any time for any reason. Patients not completing the entire study were to be fully evaluated when possible.

The patients were divided into two treatment groups. The treatment method was randomly allocated using enveloped lots picked out before the treatment. All patients were instructed to apply the adapalene gel to the whole face excluding the lips and eyelids, once a day at night after washing and moistening the facial skin. In the combination therapy group, NDFX cream was additionally applied to inflammatory acne lesions twice a day, in the morning and immediately after application of adapalene gel at night. At weeks 1 or 2 after treatment, moisturizer was added to the cases of both groups who showed dryness. The condition of acne and side-effects were monitored before and at weeks 1, 2, 4 and 8 after treatment.

Ethical approval was granted by the facility's review board of the University of Occupational and Environmental Health Japan.

Efficacy and safety assessments

The treatment efficacy was determined by percent reduction of the number of inflammatory lesions (red papules and pustules) on each half of the face. The mild or most severe acne lesions, which are defined by the Japanese acne grading system, were excluded from the evaluation. At each visit, the dermatologists counted the inflammatory lesions and observed the severity of erythema and scale on the face. The data were analyzed using the Mann–Whitney *U*-test. Erythema and scale were ranked (none, mild, moderate and severe) and analyzed using Wilcoxon rank sum tests for safety assessment.

Dryness, itch and irritation were also evaluated by visual analog scale (VAS) and analyzed using repeated measure analysis of variance.

RESULTS

A total of 50 patients (aged 12–31 years; 13 men and 37 non-pregnant women) were randomized to the two groups. The two groups were well matched with respect to demography (Table 1). The consumption of the moisturizer tended to be more in the adapalene monotherapy group (9/26 patients) than the combination therapy group (7/24 patients), but was not significantly different. After the 2-week treatment, the percent reduction of the number of inflammatory lesions on the half face was significantly higher in the combination therapy group than the adapalene monotherapy group ($P < 0.05$). The combination therapy improved inflammatory acne earlier than adapalene alone, as a significant difference in the severity was observed between the two groups at 2 weeks (Fig. 1). The

Table 1. Baseline demographic and clinical characteristics of subjects

Subjects	Adapalene and NDFX	Adapalene alone
Number (male)	24 (6)	26 (7)
Age (years)†	20.38 ± 4.88	20.46 ± 4.09
Discontinued	0	3
Severity (half face)		
Mild‡	7	15
Moderate	37	33
Severe	4	4
Consumption (g/week)†		
Adapalene	3.91 ± 0.97	3.75 ± 1.15
Moisturizer	1.77 ± 2.80	2.75 ± 3.66

†Mean ± standard deviation. ‡The half faces of patients with mild severity were excluded from this study, so that only the moderate and severe were enrolled. NDFX, nadifloxacin.

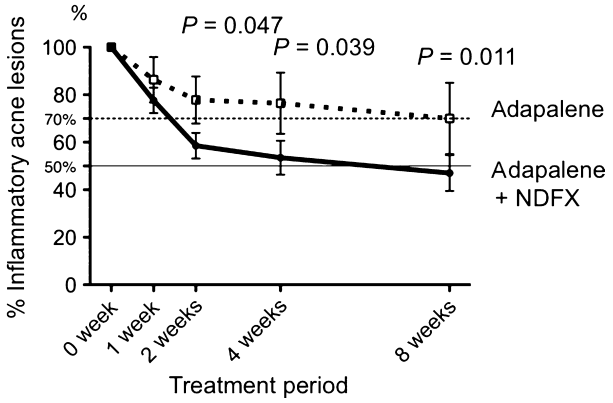

Figure 1. Alteration of inflammatory acne lesions after treatments. Patients were treated with adapalene alone or adapalene and nadifloxacin (NDFX) cream for 8 weeks. In each patient, the starting number of inflammatory acne lesions was depicted as 100%. Statistical differences between the two groups were tested using the Mann–Whitney *U*-test.

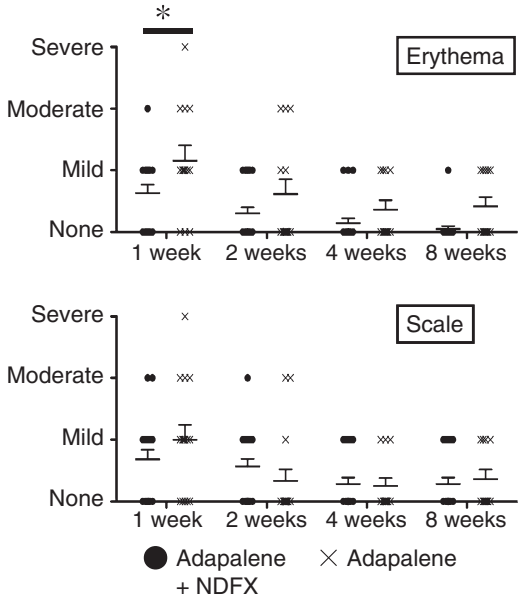

Figure 2. Adverse effects of the therapies. The side-effects of the combination therapy and the adapalene monotherapy were monitored by assessing erythema and scale during treatments. NDFX, nadifloxacin.

combination therapy reduced the number of inflammatory acne by approximately 50% at 6 weeks.

Three patients receiving adapalene monotherapy complained of burning with dryness of their faces. Despite the use of moisturizers, their symptoms were not sufficiently improved, and the study was discontinued. None of the patients in the combination group had such severe symptoms. To monitor the side-effects on the skin, erythema and scale were observed in the two groups. At 1 week after the beginning of therapy, erythema occurred at a significantly higher level in the combination therapy group (Fig. 2). The tendency of the less stimulatory action of the combination therapy was also observed at 2, 4 and 8 weeks. The levels of scale were not different between the two groups.

Results of the patients' assessments showed no significant difference between the two groups in all three skin-related events.

DISCUSSION

Acne vulgaris is recognized not only as follicular infection but also as a chronic inflammatory disease of the pilosebaceous unit. The primary pathogenic factors of acne are increased sebum production, follicular colonization of *P. acnes*, alteration in the keratinization, and release of inflammatory mediators. *P. acnes* stimulates T cells, macrophages and keratinocytes to produce inflammatory cytokines through both acquired and innate immunity.[11] Moreover, recent reports have shown that the sebaceous gland is a neuroendocrine inflammatory organ,[12] matrix metalloproteases are included in sebum[13] and oxidized lipids induce inflammatory mediators.[14] Considering these findings, combination therapy is recommended for acne, because multifaceted effects are demanded from acne treatment.

In Japan as well as other countries, adapalene combined with an antibiotic is a recent first-choice treatment for acne. The effects of adapalene for acne treatment are normalization of abnormal hyperkeratinization in the follicular infundibulum and prevention of scar formation via transcription factors, and the antimicrobial agents do not have these effects. On the other hand, antimicrobial agents exert a superior effect for inflammatory acne.[15,16] Effective combination therapies may shorten the duration of treatment.

In recent years, antibiotic resistance has become a significant public health concern in the world, including acne management.[17,18] It is thought that the quinolone derivatives have an advantage not to yield such resistant bacteria.[19] However, the use of NDFX should be used carefully also because there has been some increase in NDFX-resistant *P. acnes*.[9]

Furthermore, accumulating evidence has shown that NDFX has downmodulatory actions on immunocompetent cells. NDFX inhibits migration of neutrophils[20] and has immunomodulatory bioactivities on keratinocytes, peripheral mononuclear cells[21] and Langerhans cells.[22] Especially, NDFX inhibits production of cytokines interleukin (IL)-1, IL-6, IL-8 and γ-interferon related with acne inflammation.[21,23,24] Thus, NDFX have anti-inflammatory effects similar to the other antibiotics conventionally used for acne.[25–28]

In addition to its therapeutic effectiveness, NDFX may alleviate the adverse effect of adapalene. Adapalene is well known to induce irritation of the applied skin. In our study, three patients receiving adapalene monotherapy were unable to continue the therapy because of a burning, irritable sensation. On the other hand, none of the patients in the combination group dropped out of the study. However, it should be noted that the group on a single drug may not have had a tendency to continue a clinical trial compared with a group on two drugs when the patients knew that the other group of patients were on two drugs.

The severity of erythema in the adapalene monotherapy group was higher than that in the combination therapy group. Therefore, it seems that the combination therapy has beneficial effects not only on acne treatment but also on adapalene irritation.

In this study, we confirmed the efficacy and safety of the combination therapy with NDFX cream and adapalene for inflammatory acne. It is notable that the combination therapy improves inflammatory acne as early as 2 weeks with less irritation than adapalene monotherapy.

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