Clinical and Bacteriological Evaluation of Nadifloxacin 1% Cream Versus Erythromycin 4% Gel in the Treatment of Mild-to-Moderate Facial Acne Vulgaris: A Randomized Study

Hafif-Orta Şiddetli Akne Vulgaris Tedavisinde %1 Nadifloksasin Krem ile %4 Eritromisin Jelin Klinik ve Bakteriyolojik Olarak Değerlendirilmesi: Randomize Bir Çalışma

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ABSTRACT Objective: High percentage of *Propionibacterium acnes* resistance against erythromycin has been reported in recent years. Therefore, new antibiotic alternatives are being developed. Nadifloxacin is an effective treatment in mild-moderate acne vulgaris with antimicrobial, immunomodulatory and anti-inflammatory properties. Comparison of the clinical and bacteriological efficacy and safety of nadifloxacin 1% cream versus erythromycin 4% gel in the treatment of mild to moderate acne vulgaris was aimed. **Material and Methods:** A total of 100 patients with facial mild-moderate acne vulgaris were randomized to receive nadifloxacin 1% cream (Group I) or erythromycin 4% gel (Group II) twice daily for 12 weeks. All the patients in both groups also used topical 0.05% tretinoin twice a week at night time for 12 weeks. Both groups were compared regarding the lesion counts and global acne grading score. The growth ratios of *P. acnes* and *S. epidermidis* were evaluated. The bacterial antibiotic resistance was assessed by using the minimum inhibitory concentration values of nadifloxacin and erythromycin. **Results:** After a 12-week treatment period, both treatments caused significant similar reductions in all types of acne lesions and the global acne grading scores. Microbiological evaluation revealed no significant differences regarding the growth ratios of *P. acnes* and *S. epidermidis* in both groups. The nadifloxacin resistant *S. epidermidis* colonization was significantly higher in Group I at week 12. **Conclusion:** Nadifloxacin 1% cream is as efficacious and safe as erythromycin 4% gel in the treatment of mild to moderate acne vulgaris.

Key Words: Acne vulgaris; drug resistance, bacterial; erythromycin; microbial sensitivity tests; nadifloxacin; *Propionibacterium acnes*; *Staphylococcus epidermidis*

ÖZET Amaç: Son yıllarda eritromisine karşı yüksek oranda *Propionibacterium acnes* direnci bildirilmiştir. Bu nedenle yeni topikal antibiyotik alternatifleri geliştirilmektedir. Nadifloksasin, hafif orta şiddetli akne vulgariste antimikrobiyal, immünmodülatüar ve antiinflamatuar özellikleri ile etkin bir tedavidir. Bu çalışmada, hafif-orta şiddetli akne vulgaris tedavisinde %1 nadifloksasin krem ile %4 eritromisin jelin klinik ve bakteriyolojik olarak etkinlik ve güvenirliklerinin karşılaştırılması amaçlanmıştır. **Gereç ve Yöntemler:** Hafif-orta şiddetli akne vulgarisli toplam 100 hasta, 12 hafta boyunca, günde iki kez %1 nadifloksasin krem (Grup I) veya %4 eritromisin jel (Grup II) kullanmak üzere iki gruba randomize edildi. Her iki gruptaki tüm hastalar ayrıca, 12 hafta boyunca geceleri haftada iki gün topikal %0,05 tretinoin kullandı. Her iki grup lezyon sayısı ve global akne şiddet skoru göz önüne alınarak karşılaştırıldı. *P. acnes* ve *Staphylococcus epidermidis*'in üreme oranları değerlendirildi. Ayrıca, nadifloksasin ve eritromisinin minimum inhibitör konsantrasyon değerleri kullanılarak bakteriyel antibiyotik direnç gelişimi incelendi. **Bulgular:** Her iki tedavi de 12. haftada tüm akne lezyon tiplerinin sayımında ve global akne derecelendirme skorlarında anlamlı benzer oranda azalma sağladı. Mikrobiyolojik değerlendirmede, her iki grupta da *P. acnes* ve *S. epidermidis* üreme oranlarında istatistiksel olarak anlamlı bir fark görülmedi. On ikinci haftada nadifloksasine dirençli *S. epidermidis* kolonizasyonu Grup I'de istatistiksel olarak anlamlı oranda daha fazla idi. **Sonuç:** Hafif-orta şiddetli akne vulgaris tedavisinde %1 nadifloksasin krem, %4 eritromisin jel kadar etkili ve güvenilirdir.

Anahtar Kelimeler: Akne vulgaris; ilaç direnci, bakteriyel; eritromisin; mikrobiyal duyarlılık testleri; nadifloksasin; *Propionibacterium acnes*; *Staphylococcus epidermidis*

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Erythromycin is a macrolide antibiotic which is still among the most frequently prescribed topical acne medications due to its potent antibacterial and anti-inflammatory activities.[1] Yet, a high percentage (20-65%) of bacterial resistance against erythromycin has been reported.[2] Nadifloxacin, an anti-bacterial agent from fluoroquinolone group, has a high bactericidal activity against *Propionibacterium acnes* (*P. acnes)* that plays an important role in the pathogenesis of acne vulgaris (AV). Its broad spectrum also covers *Staphylococcus epidermidis (S. epidermidis)*.[3,4]

There are only a few studies in literature that compares the clinical and microbiological efficacy of nadifloxacin versus erythromycin.[5-7]

The present study was undertaken to compare both the clinical and microbiological efficacy and safety of a combination therapy of topical 1% nadifloxacin and 0.05% tretinoin versus topical 4% erythromycin and 0.05% tretinoin in the treatment of mild to moderate AV.

MATERIAL AND METHODS

The study was approved by Başkent University Institutional Review Board, and all participants gave informed consent before study participatition.

STUDY POPULATION

This study included 100 consecutive patients with a diagnosis of mild to moderate AV (73 female and 27 male) who attended Dermatology Department of Başkent University in Ankara, Turkey, between May and July 2009. Subjects were excluded from the study if they had been taking systemic retinoids in the previous 6 months, oral contraceptives in the past 3 months, systemic antibiotics or topical acne medications within a previous month. Pregnant or lactating women, patients with hormonal disorders such as PCOS were also excluded from the study.

STUDY DESIGN

In this prospective study, patients were randomized into 2 groups. Group I (n=56) applied topical 1% nadifloxacin (Nadixa cream®, Adeka Pharmaceuticals, Samsun, Turkey) twice daily and topical 0.05% tretinoin (Tretin cream®, Assos Pharmaceuticals, Turkey) twice a week at night time, while Group II (n=55) applied topical 4% erythromycin (Acnilox gel®, Assos, Turkey) twice daily and topical 0.05% tretinoin twice a week at night time. All the topicals were applied to whole face for 12 weeks. The patients were evaluated at baseline and biweekly intervals during treatment period by the same investigator.

EFFICACY ASSESSMENT

Clinical severity of AV was assessed using 2 different scoring methods namely the "Lesion count" and the "Global Acne Grading Score (GAGS)".[8] In each patient, different images with frontal, right and left profiles were taken.

THE LESION COUNT

At each visit, total number of non-inflammatory lesions namely open and closed comedones (TNIL) and total inflammatory lesions namely papules and pustules (TIL) were counted on the face. Yet, comedones located on the nose were not included to TNIL.

THE GLOBAL ACNE GRADING SCORE

At baseline and weeks 2 and 12 of treatment, GAGS was performed (Figure 1). It was measured by addition of the local scores for 5 different areas on the face like forehead, right and left cheek, nose and chin. The local score was measured by

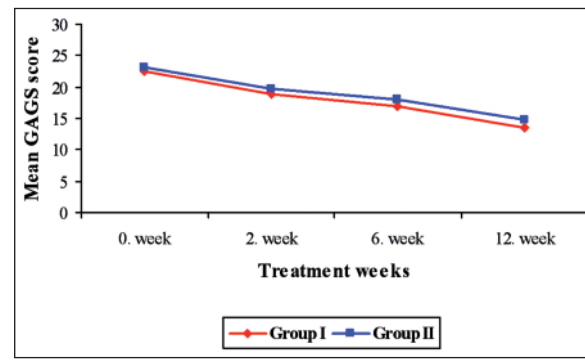

FIGURE 1: The change of the global acne grading scores (GAGS) of the patients in nadifloxacin and erythromycin groups.

multiplying a factor (1-3) defined according to the localization and the lesion severity score (0-4 points). This factor was defined as 2 in forehead, 2 in right and left cheek, 1 in nose and 1 in chin. The lesion severity score was described as follows; If no lesion exists; 0 point, merely comedones; 1 point, papules; 2 points, pustules; 3 points, nodules; 4 points. If the calculated total value was between 1 and 18, acne severity was scored as mild, while if it is between 19 and 30, it was accepted as moderate.[8]

PATIENTS' ASSESSMENT OF TREATMENT EFFICACY

At the end of treatment, all participants answered the question "How do you evaluate the change in your disease since you started the treatment?" as either got worse, no change, good improvement or very good improvement.

CLINICIAN'S ASSESSMENT OF TREATMENT EFFICACY

The clinician evaluated the final change in the severity of the AV compared to the pretreatment as got worse, no change (≤25% improvement), good improvement (25-75% improvement) or very good improvement (>75% improvement).

EVALUATION OF THE SIDE-EFFECTS

The presence of local dermatological side effects namely erythema, dryness, burning or sensation of warmth, itching, hypo- or hyperpigmentation were noted at weeks 2, 6 and 12 of treatment.

MICROBIOLOGICAL ANALYSIS

At pre- and post-treatment visits, skin swabs were taken from the surface of a predetermined part of the face such as forehead or cheek for bacteriological cultures. Samples were taken from a papulopustuler lesion at baseline and from a comedone in case of all inflammatory lesions were cleared at the end of the treatment.

Isolates of *P. acnes* were identified using the API 20A multi-test identification system (BioMérieux, Basingstoke, England), while coagulase-negative staphylococci isolates were identified as *S. epidermidis* by Staph ID32 API system (BioMérieux, Basingstoke, England).

ANTIBIOTIC SUSCEPTIBILITY TEST

Minimum inhibitory concentration (MIC) of erythromycin for *P. acnes* and *S. epidermidis* were determined by the agar dilution method according to Clinic and Laboratory Standards Institute (CLSI) criteria. MIC values of erythromycin and nadifloxacin were determined as the lowest concentration of antimicrobials in which no bacterial growth was observed in agar dilution plaques after 24 hours for *S. epidermidis* and after 48 hours for *P. acnes*. According to the CLSI, the MIC value of erythromycin for *S. epidermidis* was accepted as susceptible if it was ≤0.5 μg/mL, moderately susceptible if it was 0.5< and<8 μg/mL and resistant if it was ≥ 8 μg/mL.[9] Since the CLSI has not yet approved the breakpoints of erythromycin for *P. acnes,* we used the European Committee in Antibiotic Susceptibility Test (EUCAST) guidelines as the reference for the antibiotic susceptibility tests. If the MIC value of erythromycin for the *P. acnes* was <0.5 μg/mL, it was regarded as susceptible, and if it was ≥0.5 μg/mL, it was accepted as resistant.[10] As nadifloxacin is a new antibiotic, there is no MIC breakpoints for any of the bacteria yet. Therefore, in our study the breakpoints of nadifloxacin for both *S. epidermidis* and *P. acnes* were accepted as the reference value assumed in a study investigating the bacterial resistance ratios of topical 1% nadifloxacin and 2% erythromycin. If the value is ≥ 0.5 μg/mL, then it was accepted as resistant.[5]

STATISTICAL ANALYSES

SPSS Statistics 11.5 (SPSS, Chicago, IL, USA) was used for the statistical analysis. During the evaluation of the data obtained from the study, descriptive statistical methods of mean, standard deviation, and frequency and ratio values were used in the tables. Mann-Whitney *U* test was used for the comparison of the variables that have non-normal distributions. Chi-square test was used for the comparison of the nominal variables between two groups.[11] Friedman test was used to compare the variables within each group. Comparison of the nominal variables within each group was assessed by McNemar test. The results were evaluated at a

95% confidence interval (CI) and at a significance level of $p<0.05$.

RESULTS

There were 38 (76%) female and 12 (24%) male in Group I, while Group II consisted of 35 (70%) female and 15 (30%) male. The mean age in Group I was 22.9±4.4 (range, 16-30) years, and in Group II, it was 22.3±4.5 (range, 16-30) years. No significant difference was noted in the mean age and sex distribution between the two groups (p=0.424 and p=0.499, respectively). Furthermore, no significant differences were observed with regard to the duration and severity of acne defined by total number of lesions and the GAGS scores (Table 1).

TABLE 1: Demographic features of the patients in nadifloxacin and erythromycin groups.

		Group I (Nadifloxacin) n=50	Group II (Erythromycin) n=50	p
Age (year)		22.9±4.4	22.3±4.5	[a]0.424
Sex	Female	38 (76%)	35 (70%)	[b]0.499
	Male	12 (24%)	15 (30%)	
Acne duration (month)		66.5±42.8	66.02±47.8	[a]0.813
Acne severity	Mild	9 (18%)	8 (16%)	[b]0.790
	Moderate	41 (82%)	42 (84%)	
GAGS score		22.6±3.9	23.2±4.6	[a]0.445

GAGS: Global acne grading score.
[a]Mann Whitney U test is used [b]Chi-square test was used.

CLINICAL EFFICACY EVALUATION

Both treatment groups indicated a significant reduction in the mean number of all types of acne lesions and GAGS scores at the end of the study.

THE LESION COUNT

The decrease in the number of TNIL was 79% in Group I and 80% and in Group II. The number of TIL reduced in 59% and 66% of the patients in Group I and Group II, respectively. There was no statistically significant difference between 2 groups at the end of the treatment regarding reductions in TNIL and TIL ($p>0.05$ and $p>0.05$, respectively) (Table 2).

THE GLOBAL ACNE GRADING SCORE

The post-treatment decrease in the mean values of GAGS were 40% and 37% in Group I and Group II, respectively ($p<0.05$) (Table 3). There was no significant difference regarding the GAGS values of both groups at weeks 0, 2, 6 and 12 of treatment ($p>0.05$).

PATIENTS' ASSESSMENT OF TREATMENT EFFICACY

At the end of treatment, the results of the patients' assessment of treatment efficacy in Group I was statistically significantly better than Group II (p=0.031). None of the patients in Group I, while 2 patients in Group II reported that, their acne did not change or got worse. All the patients in Group I and 48 patients in Group II reported a good or a very good improvement.

CLINICIAN'S ASSESSMENT OF TREATMENT EFFICACY

No difference was found in the clinician's assessment of the treatment efficacy between the two groups (p=0.895).

EVALUATION OF THE SIDE-EFFECTS

Side effects were noted in 46 patients (92%) in Group I and in 48 patients (96%) in Group II. Dryness was the most common one observed in both groups yet it was more frequent in Group II than in Group I (p=0.019). Three patients in Group I and 6 patients in Group II had a treatment interruption for 2 days due to irritant contact dermatitis. No patients reported systemic side effects.

THE MICROBIOLOGICAL INVESTIGATION

At baseline, no statistically significant differences were found in *P. acnes* and *S. epidermidis* growth ratios (p=0.204 and p=1.000 for group I and II, respectively). Microbiological evaluation revealed no significant differences regarding the growth ratios of *P. acnes* and *S. epidermidis* in either group at 12th week (p=1.000 and p=0.053 for Group I and II, respectively). However, growth ratio of *S. epidermidis* decreased significantly in Group I at the completion of the treatment. (p=0.002) (Table 4).

The comparison of the values of MIC_{median}, and MIC 25-75% percentiles of nadifloxacin and

TABLE 2: The mean number of the open comedones, closed comedones, papules and pustules at baseline and at the end of 2nd, 4th, 6th, 8th, 10th and 12th weeks (mean number±SD) and the percentage of the reduction in mean number of the lesions as compared to baseline values in nadifloxacin and erythromycin groups.

		Group I (Nadifloxacin)		Group II (Erythromycin)	
Weeks	**Parameters**	**Mean±SD, median**	**% reduction**	**Mean±SD, median**	**% reduction**
Baseline	Open comedones	41.08±35.74, 30.50		34.14±34.51, 24.50	
	Closed comedones	50.40±33.13, 43.50		47.38±28.08, 42.50	
	Papules	4.44±2.82, 4.00		5.06±3.46, 4.50	
	Pustules	2.40±2.69, 2.00		2.84±3.34, 2.00	
Week 2	Open comedones	25.40±25.77, 17.50	39.04	20.44±17.94, 15.50	40.12
	Closed comedones	34.42±32.71, 25.00	31.70	27.86±17.83, 22.00	41.19
	Papules	2.32±1.91, 2.00	47.74	3.10±2.73, 3.00	38.73
	Pustules	1.26±1.57, 1.00	47.5	1.58±2.03, 1.00	44.36
Week 4	Open comedones	17.06±18.38, 11.00	32.83	16.56±20.12, 12.50	18.98
	Closed comedones	26.64±25.88, 19.00	22.60	19.80±13.34, 16.00	28.93
	Papules	1.88±1.66, 1.50	18.96	2.32±2.33, 2.00	25.16
	Pustules	1.12±1.36, 1.00	11.11	1.46±1.83, 1.00	7.59
Week 6	Open comedones	12.98±15.70, 7.50	23.91	14.12±17.05, 9.00	14.73
	Closed comedones	21.42±23.28, 15.00	19.59	16.64±12.79, 12.50	15.95
	Papules	1.86±1.89, 1.00	1.06	2.02±2.18, 2.00	12.93
	Pustules	1.04±1.56, 1.00	7.14	1.26±1.48, 1.00	13.69
Week 8	Open comedones	10.72±14.09, 5.00	17.41	11.88±15.43, 7.00	15.86
	Closed comedones	16.98±18.16, 13.00	20.72	12.34±9.58, 9.50	25.84
	Papules	2.36±2.55, 2.00	+21.18	2.02±2.64, 1.00	0
	Pustules	0.82±1.24, 0.00	21.15	1.00±1.42, 0.00	20.63
Week 10	Open comedones	9.70±13.09, 5.00	9.51	9.66±13.27, 6.00	18.68
	Closed comedones	13.46±16.24, 10.00	20.73	9.98±9.09, 7.00	19.12
	Papules	2.44±2.65, 2.00	+3.27	2.12±2.32, 2.00	+4.71
	Pustules	0.84±1.40, 0.00	2.38	0.76±1.13, 0.00	34
Week 12	Open comedones	8.20±12.20, 3.00	15.46	7.48±11.16, 4.00	22.56
	Closed comedones	11.14±14.39, 6.00	10.65	8.04±8.02, 5.00	19.43
	Papules	2.18±2.63, 1.00	10.65	2.16±2.52, 1.00	+1.85
	Pustules	0.62±1.33, 0.00	26.19	0.50±0.88, 0.00	34.21

Mann Whitney U Test Friedman test

TABLE 3: The mean and median values of global acne grading scores of the patients in nadifloxacin and erythromycin groups.

	Group I (Nadifloxacin) (n=50)	Group II (Erythromycin) (n=50)	
GAGS score	**mean±SD, median (min.-max.)**	**mean±SD, median (min.-max.)**	**[a]p**
Week 0	22.60±3.93, 23.00 (15-30)	23.20±4.57, 23.50 (14-30)	0.445
Week 2	18.92±4.68, 19.00 (10-32)	19.72±5.64, 19.00 (6-31)	0.498
Week 6	16.86±5.27, 16.00 (5-29)	18.06±5.79, 17.50 (8-31)	0.369
Week 12	13.58±5.64, 13.00 (4-27)	14.68±5.12, 14.50 (3-30)	0.231
[b]p*	0.000	0.000	

p* shows comparison of week 0 and week 12.

GAGS: Global acne grading score

[a]:Mann Whitney U test was used. [b]:Friedman test was used.

TABLE 4: The growth ratios of *P. acnes* and *S. epidermidis* before and after the treatment in nadifloxacin and erythromycin groups.

Microbiological culture	Group I (Nadifloxacin) (n=50) Growth (+)	Group II (Erythromycin) (n=50) Growth (-)	[a]p
P. acnes			
Before treatment	45 (90%)	49 (98%)	0.204
After treatment	50 (100%)	49 (98%)	1.000
[b]p*	0.063	1.000	
S. epidermidis			
Before treatment	48 (96%)	48(96%)	1.000
After treatment	35 (70%)	43 (86%)	0.053
[b]p*	0.002	0.180	

P. acnes: *Propionibacterium acnes*

S. epidermidis: *Staphylococcus epidermidis*

p* shows comparison of the growth ratios of *P. acnes* and *S. epidermidis before* and after the treatment in each group.

[a]Chi-square test was used. [b]Mc-Nemar test was used.

erythromycin for *P. acnes* and *S. epidermidis* at weeks 0 and 12 in Group I and Group II are shown in Table 5. At baseline, MIC_{median} values of nadifloxacin and erythromycin for *P. acnes* and *S. epidermidis* were similar in both groups. At the end of the treatment, MIC_{median} values of both antibiotics were similar for *P. acnes*. However, MIC_{median} value of nadifloxacin for *S. epidermis* was statitistically significantlly higher in Group I than Group II (p=0,001) (Table 5). The increase in the MIC_{median} value of erythromycin for *S. epidermidis* was also statistically significantly higher in Group II than Group I at the end of the treatment (p=0,012) (Table 5).

ANTIBIOTIC SUSCEPTIBILITY TEST RESULTS

At baseline, nadifloxacin resistant *P. acnes* and *S. epidermidis,* and erythromycin resistant coloniza-

TABLE 5: The comparison of the median and 25-75% percentile values of MIC of nadifloxacin and erythromycin for *P. acnes* and *S. epidermidis* at week 0 and 12 in nadifloxacin and erythromycin groups.

				Group I (Nadifloxacin)	Group II (Erythromycin)	p
P. acnes	Nadifloxacin MIC (µg/mL)	Week 0	n Median Perc 25-75%	45 0,06 0,03-0,06	49 0,06 0,03-0,06	**0,656**
		Week 12	n Median Perc 25-75%	45 0,25 0,03-1,0	44 0,13 0,03-0,25	**0,243**
	Erythromycin MIC (µg/mL)	Week 0	n Median Perc 25-75%	45 0,06 0,03-0,75	49 0,06 0,05-6,0	**0,356**
		Week 12	n Median Perc 25-75%	50 0,25 0,06-64	49 0,25 0,06-24,0	**0,683**
S. epidermidis	Nadifloxacin MIC (µg/mL)	Week 0	n Median Perc 25-75%	49 0,03 0,03-0,03	47 0,03 0,03-0,03	**0,463**
		Week 12	n Median Perc 25-75%	34 64 16-64	43 0,13 0,03-16	**0,001****
	Erythromycin MIC (µg/mL)	Week 0	n Median Perc 25-75%	49 64 0,25-64	47 16 1-64	**0,656**
		Week 12	n Median Perc 25-75%	34 64 7-64	43 64 64-64	**0,012***

P. acnes: Propionibacterium acnes; *S. epidermidis: Staphylococcus epidermidis.*

MIC (µg/mL)±SD: Minimum inhibitory concentration±Standart deviation

*p<0.05 statistically significant

Mann Whitney U test was used.

tions were similar in both groups. On the completion of the treatment although no significant difference was observed in the number of the erythromycin resistant *P. acnes* and *S. epidermidis* colonizations, nadifloxacin resistant *S. epidermidis* colonization was statistically significantly higher in Group I (n=31, 91.2%) than Group II (n=18 (41.9%) (p=0.000). Nadifloxacin resistant *P. acnes* colonization was also similar (p>0.05).

DISCUSSION

The most important finding in this study was the similar clinical and microbiological efficacy achieved in both treatment groups. In literature, there are only a few studies that investigated the clinical and microbiological efficacy of topical nadifloxacin in the treatment of AV.[5-7] A multi-centre double blind study conducted by Bojar et al., consisted of 86 patients with mild-moderate AV revealed that topical 1% nadifloxacin and 2% erythromycin have similar clinical efficacy on the number of the TIL and TNIL after a 12 week treatment period.[5] In another multi-centered, double blind study by Plewig et al., nadifloxacin 1% cream was compared with erythromycin 2% cream in 474 European patients with predominantly inflamed slight-to-moderate AV. During 12 weeks of treatment both nadifloxacin and erythromycin caused significant reduction in the number of inflamed papulo-pustular lesions.[6] Tunca et al. also reported similar clinical results regarding the efficacy of topical 1% nadifloxacin versus topical 4% erythromycin.[12] They described that there had been a significant reduction in lesion counts and acne severity index scores beginning from the first visit at week 4. This reduction had continued throughout the 12-week study period. We believe that the absence of the control groups in this study is the limitation of this study. Although these two groups showed therapeutic effects, as there were no control groups included in the study it is difficult to determine the exact clinical effect of either antibiotics or tretinoin.

In the present study, significant clinical improvements in TIL and TNIL counts were achieved at every visit, in accordance with the previous studies.[5,6,12] Plewig et al. reported that according to the patients' assessments of both treatments were analogous in their study, but tolerance of the patients to adverse effects was better in nadifloxacin group.[6]

In current study, patients in nadifloxacin group assessed treatment efficacy better than the ones in erythromycin group. This might be associated with the less frequent occurrence of side effects such as dryness in this group. Furthermore, clinician's assessment results were alike with the results of lesion counts and GAGS in both groups.

As monotherapy with topical antibiotics is not recommended in the treatment of AV in order to avoid the occurrence of acquired antibiotic resistance, topical 0.05% tretinoin was applied twice a week at night time in both groups.[13] The higher frequency of dryness observed in this study compared with the previous studies, may be due to the addition of topical tretinoin to antibiotic therapy. Since the main side effects of topical tretinoins are skin dryness and erythema.[14] Yet, although both groups were treated with topical tretinoin, erythromycin prescribed subjects had dryness more frequently. We should also take into account of the higher concentration of erythromycin (4%) used in this study compared with the ones (2%) used in former studies.[5,6] Moreover, Tunca et al. reported similar frequencies of side effects (30.2% and 27.9%, respectively) observed in their subjects treated either with 1% nadifloxacin or 4% erythromycin.[12] In our study, at the 2nd week of the treatment, 30% of the participants in nadifloxacin group reported a burning sensation, while only 8% of the patients in erythromycin group had it. As no significant difference was observed between the groups in the following weeks, we think that the burning sensation was a just temporary reversible side effect.

Since we did not find any significant difference in the growth ratios of *P. acnes* in both groups both before and after the treatment, we think both treatments have similar antibacterial efficacy against *P. acnes.* The reason for the statistically significant decrease of *P. acnes* growth in earlier studies may be due to the differences in bacterial

resistances across different countries.[6] In recent years, it has been generally accepted that the quantitative amount of *P. acnes* growth rather than its presence is associated with the clinical improvement in AV.[15] Furthermore, in the study by Bojar et al., quantitative methods that reflect the amount of the total viable bacterial colonies were also used.[5] In this study, although we could not determine a significant difference in the growth ratios of *S. epidermidis* in the erythromycin group, it seems that nadifloxacin may have a better anti-bacterial efficacy against *S. epidermidis* than erythromycin. However, the significantly higher nadifloxacin resistant *S. epidermidis* colonization found in nadifloxacin group at the end of the treatment do not exactly prove us the microbiological priority of nadifloxacin. Besides the final growth ratios of *S.epidermidis* at the end of the study were also analogous. These contrary results should be examined in further comprehensive studies. In the management of a variety of infectious diseases especially in urinary tract, the quinolone resistance is a very commonly encountered problem resulting from the intensive use of quinolone antibiotics.[16] However, the ratios of nadifloxacin resistances were found to be similar in Germany where topical nadifloxacin have been used for a few years and in Spain where topical nadifloxacin has not been prescribed too often.[17] A clinical study of Ueno et al., reported no nadifloxacin resistant *P. acnes* species.[18] On the contrary, some antibiotics such as erythromycin and clindamycin; mostly used in AV management frequently cause *P. acnes* resistance.[19-21] In another study by Nishijima et al., although the resistance of *P. acnes* to erythromycin was reported as non-significant, 30% of the *S. epidermidis* species were reported to be resistant to erythromycin.[19] However, we did not observe a significant increase in erythromycin resistance against *P. acnes*. The variety of the bacterial resistances in different countries may be due to the varieties of the bacterial flora in different communities which is mostly related to the frequency of prior antibiotic use.

CONCLUSION

Our data revealed that nadifloxacin 1% cream is as efficacious and safe as erythromycin 4% gel in the treatment of acne lesions. Therefore, topical nadifloxacin can be regarded as a good treatment option in the management of mild to moderate AV.

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