Original Investigation
Orijinal Araştırma

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Comparison of dapsone gel and nadifloxacin cream in the adjuvant treatment of acne vulgaris patients on systemic isotretinoin therapy: A retrospective study

Sistemik izotretinoin tedavisi alan akne vulgaris hastalarında yardımcı tedavi olarak dapson jel ve nadifloksasin kremin karşılaştırılması: Bir retrospektif çalışma

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Abstract

Background and Design: We aimed to compare the additional impact of dapsone gel and nadifloxacin cream as adjuvant treatments with systemic isotretinoin for moderate and severe acne vulgaris.
Materials and Methods: We retrospectively compared patients with moderate-to-severe acne vulgaris who received dapsone 7.5% gel or nadifloxacin 1% cream in combination with oral isotretinoin treatment at Altunizade and Ataşehir Acıbadem Hospitals between January 2021 and October 2023. Isotretinoin treatment was administered at fixed low doses of 10-30 mg/day alongside topical treatments until the lesions resolved. Thereafter, oral isotretinoin was continued as monotherapy for an additional two months after the clearance of active lesions.
Results: A total of 74 patients, 34 in the dapsone group (24 female, 10 male) and 40 in the nadifloxacin group (21 female, 19 male), were included in the study. The time to complete clearance of active lesions and the total treatment time were significantly shorter in the dapsone group (2.68±0.18 and 5.15±0.14 months, respectively) than in the nadifloxacin group (3.43±0.15 and 5.8±1.9 months, respectively). The cumulative dose of isotretinoin was significantly lower in the dapsone group (3376.5±71.9 mg) than in the nadifloxacin group (4155±88.4 mg). Skin dryness was observed more frequently in the dapsone group (29.4% vs. 12.5%), but this difference was not statistically significant (p=0.071).
Conclusion: Topical dapsone gel may be an effective adjuvant therapy to accelerate the treatment response to oral isotretinoin and reduce the cumulative dose of isotretinoin. However, larger prospective studies are needed to determine the optimal adjuvant treatment options.
Keywords: acne, nadifloxacin, dapsone, isotretinoin

Öz

Amaç: Dapson jel ve nadifloksasin kremin sistemik izotretinoin tedavisine adjuvan olarak orta ve şiddetli akne vulgariste etkisini karşılaştırmaktır.
Gereç ve Yöntem: Altunizade ve Ataşehir Acıbadem Hastanesi'nde Ocak 2021 ve Ekim 2023 tarihleri arasında oral izotretinoin tedavisine adjuvan olarak dapson %7,5 jel veya %1 nadifloksasin krem kullanan orta ve şiddetli akne vulgaris hastalarının tedavi sonuçları retrospektif olarak karşılaştırıldı. Aktif lezyonların tam kontrolüne kadar günde 10-30 mg sabit düşük dozda, topikal tedavilerle kombine olarak verilen izotretinoin tedavisine, aktif lezyonların tam gerilemesinin ardından iki ay süreyle monoterapi olarak devam edildi.
Bulgular: Çalışmaya dapson grubunda 34 (24 kadın, 10 erkek), nadifloksasin grubunda 40 olmak üzere (21 kadın, 19 erkek) toplam 74 hasta dahil edildi. Aktif lezyonların tam gerileme süresi ve toplam tedavi süresi dapson grubunda (sırasıyla 2,68±0,18 ve 5,15±0,14 ay) nadifloksasin grubuna (sırasıyla 3,43±0,15 ve 5,8±1,9 ay) göre anlamlı olarak daha kısaydı. Kümülatif izotretinoin dozu da dapson grubunda (3376,5±71,9 mg) nadifloksasin grubuna göre (4155±88,4 mg) anlamlı düşük bulundu. Deri kuruluğu dapson grubunda daha sık izlenmesine rağmen (%29,4 vs %12,5) fark anlamlılığa ulaşmadı (p=0,071).
Sonuç: Topikal dapson jel, oral izotretinoin tedavi yanıtını hızlandırmak ve kümülatif izotretinoin dozunu düşürmek için etkili bir adjuvan tedavi olabilir. Bununla birlikte, optimal adjuvan tedavi seçeneklerini belirlemek için daha geniş prospektif çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: akne, nadifloksasin, dapson, izotretinoin

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Introduction

Acne vulgaris (AV) is a chronic inflammatory disease that affects the pilosebaceous unit. It is one of the most common dermatological diseases, particularly in adolescents and young adults, affecting up to 85% of adolescents[1,2]. Acne pathogenesis is based on the change in hormonal balance during puberty and its impact on pilosebaceous gland function. Hyperkeratinization in the follicular epithelium and increased sebum synthesis resulting from increased androgen levels pave the way for comedone formation. Changes in normal skin flora, particularly the overgrowth of *Cutibacterium acnes*, can cause an increase in inflammatory cytokines such as interleukin (IL)-1. This, along with comedone rupture, leads to inflammation spreading to the dermis, resulting in inflammatory acne lesions such as papules, pustules, nodules, and cysts[1].

Benzoyl peroxide, azelaic acid, topical retinoic acid derivatives, salicylic acid, and topical antibacterial products such as topical clindamycin, erythromycin, dapsone, minocycline, sodium sulfacetamide, and their various combinations are recommended as first-line treatments for mild to moderate acne[2]. For moderate and severe acne, oral antibiotics in combination with topical treatments may be a treatment option[2]. Oral isotretinoin is the most effective treatment for acne and is recommended for patients with severe nodulocystic acne or resistance to conventional treatments. Despite its high effectiveness, it has a wide range of adverse effects, which are mostly dose-dependent, such as dryness, cheilitis, elevated aminotransferase levels, and myalgias[2,3]. Recently, studies have been conducted on reducing the dosage and duration of isotretinoin treatment due to safety concerns. Studies indicate that low-dose isotretinoin treatment (<0.5 mg/kg/day) might be as effective as standard-dose treatment, with fewer dose-dependent side effects[3].

Dapsone is a sulfone drug with anti-inflammatory and antimicrobial effects. Although oral dapsone is effective in treating acne, systemic side effects such as anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, dapsone hypersensitivity, and agranulocytosis limit its use[4,5]. Dapsone gel at concentrations of 5% and 7.5% is Food and Drug Administration-approved for treating acne in patients over 12 years of age[4]. Dapsone gel has been reported to be safe in patients with G6PD deficiency, although caution is recommended when used in combination with oral treatments such as trimethoprim/sulfamethoxazole and antimalarials. The most common side effects are erythema, dryness, burning sensation, and peeling, which are usually observed locally in the application area.

Nadifloxacin, a topical fluoroquinolone antibiotic, is a broad-spectrum antibacterial agent effective against many aerobic and anaerobic bacteria that cause skin infections and AV. Besides its antibacterial properties, it has been suggested to be effective in treating acne by inhibiting pro-inflammatory cytokines[6].

In clinical practice, low-dose isotretinoin therapy is often combined with various topical treatments such as clindamycin, betamethasone, benzoyl peroxide, and tretinoin[3]. However, there is a paucity of studies in the literature evaluating and comparing the efficacy of adjuvant topical treatments, leaving a gap in determining a safe adjuvant therapy that accelerates the response to isotretinoin while inhibiting exacerbations[3]. The aim of this study was to compare the additional effects of dapsone gel and nadifloxacin cream as adjunctive treatments to systemic isotretinoin in moderate and severe AV.

Material and Methods

In this study, AV patients who received dapson 7.5% gel or nadifloxacin 1% cream as topical adjuvant treatment with oral isotretinoin at Altunizade and Ataşehir Acıbadem Hospitals, İstanbul, Türkiye, from January 2021 to October 2023 are retrospectively evaluated.

In light of the studies demonstrating the efficacy of low-dose isotretinoin regimens in moderate and severe acne[7-12], in our clinical practice, isotretinoin treatment was administered at a fixed low-dose of 10-30 mg/day to patients with moderate and severe AV, based on their Global Acne Assessment Score (GAAS), with the objective of minimizing adverse effects. Patients eligible for isotretinoin treatment were given adjuvant topical anti-acne treatments until facial acne lesions were clear, and isotretinoin monotherapy was continued for another 2 months.

Prior to the launch of dapsone 7.5% gel in Türkiye in April 2022, nadifloxacin 1% cream was our preferred adjuvant therapy, in combination with oral isotretinoin, for treating patients with AV. However, with the availability of dapsone gel, it has become a viable alternative to nadifloxacin for patients with acne receiving oral isotretinoin therapy. Dapsone 7.5% gel was applied once daily, whereas nadifloxacin 1% cream was applied twice daily as a thin layer on the entire face. Short-term anti-inflammatory antibiotic treatment was administered to both groups to control exacerbations if necessary. None of the patients had clinically suggestive gram-negative folliculitis.

In this retrospective study, data of patients who met the inclusion criteria were accessed from their records. Patients with very severe acne, any metabolic disease, or those using concurrent systemic therapy or other topical medications on the facial area were excluded. Patient demographic characteristics, acne severity, previous isotretinoin use, clinical clearance time, cumulative isotretinoin dose, total treatment duration, and side effects were recorded. The following definitions were used to categorize GAAS subgroups: One (almost clear): Rare non-inflammatory lesions with sparse non-inflamed papules. Two (Mild): Few inflammatory lesions with some non-inflammatory lesions (no nodulocystic lesions). Three (Moderate): Multiple inflammatory lesions with a predominance of non-inflammatory lesions. Four (Severe): Numerous inflammatory lesions, many comedones, and a few nodulocystic lesions. Five (Very severe): Predominance of high-inflammatory lesions and multiple nodulocystic lesions. Skin dryness was assessed based on patient self-reports.

Ethics

This study was approved by the Acıbadem University and Acıbadem Health Institutions Medical Research Ethics Committee (ATADEK) with decision number 2024-1/26, date: 25.01.2024.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS version 26. A chi-square test was employed for the comparison of categorical data, a Student's t-test was used for the comparison of continuous data exhibiting a normal distribution, and a Mann-Whitney U test was utilized for the comparison of continuous data not exhibiting a normal distribution. A significance level of $p<0.05$ was applied to all tests.

Results

The study included 74 patients who received oral isotretinoin with adjuvant topical treatment for moderate or severe AV according to the GAAS criteria. The dapsone and nadifloxacin groups comprised 34 (24 women, 10 men) and 40 patients (21 female, 19 male), respectively. The mean age was 22.03 (±0.84) years in the dapsone group and 24.13 (±0.72) years in the nadifloxacin group. Of the participants, 67.6% (23/34) in the dapsone group and 60% (24/40) in the nadifloxacin group had severe AV. In the dapsone group, 8.8% (3/34) of patients had previously used systemic isotretinoin therapy, compared with 10% (4/40) in the nadifloxacin group. There were no significant differences between the groups in terms of disease severity, sex, or frequency of previous isotretinoin use.

The clinical clearance time was significantly shorter in the dapsone group (2.68±0.18 months) than in the nadifloxacin group (3.43 months ±0.15) (p=0.000).

The study revealed that the dapsone group received a significantly lower cumulative isotretinoin dose (3376.5±71.9 mg) and had a shorter treatment duration (5.15±0.14 months). The nadifloxacin group, on the other hand, received a cumulative isotretinoin dose of 4155±88.4 mg and had a treatment duration of 5.8±1.9 months (p=0.000 and p=0.009, respectively).

The treatment was well tolerated in both groups. Eight of 34 patients (23.5%) reported discomfort with the dapsone gel base leaving residue on their faces. Dryness was observed in 29.4% (10/34) and 12.5% (5/40) of patients in the dapsone and nadifloxacin groups, respectively. No significant difference was found in the frequency of dryness (p=0.071). The demographic and clinical characteristics of the study groups are summarized in Table 1.

Discussion

This study retrospectively compared the efficacy of topical dapsone and topical nadifloxacin treatments combined with fixed low-dose isotretinoin. The results indicated that the combination of isotretinoin with dapsone significantly reduced the time to lesion clearance, total treatment duration, and cumulative isotretinoin dose.

Topical treatments are frequently used as monotherapy or in combination for acne management[13]. Dapsone gel is recommended to be used twice a day at 5% concentration and once a day at 7.5% concentration. In placebo-controlled studies, treatment effectiveness started in the 2nd week, reached significance in the 4th week, and its effect on inflammatory lesions was more pronounced than on non-inflammatory lesions. One study reported that dapsone 5% gel was more effective in women than in men[14]. At the 12th week, dapsone 7.5% gel resulted in a significant reduction of approximately 50% in the total number of acne lesions among patients with moderate acne. Additionally, it achieved a success rate of approximately 30% in GAAS scores[4,15,16]. The combination of dapsone 5% gel with tazarotene 0.1% cream demonstrated a 63.3% reduction in the total number of acne lesions (inflammatory and non-inflammatory) at 12 weeks. This combination was significantly more effective in treating comedonal acne than tazarotene 0.1% cream used alone[17].

A split-face prospective study evaluating 34 patients showed that nadifloxacin cream twice-a-day treatment provided a 70% and 48% reduction in inflammatory lesions and non-inflammatory lesions in 8 weeks, respectively, and a significant decrease in inflammation and IL-8 levels in histopathological examination[18]. A prospective study comparing the combination of nadifloxacin 1% cream and adapalene 0.1% gel with adapalene 0.1% gel monotherapy found that control of inflammatory lesions was superior in the combination group from week 4, reaching 66% efficacy at week 12. Additionally, dryness was significantly lower in the combination group[19].

Comparative studies have found isotretinoin treatment to be superior to placebo, oral antibiotics, and other controls, with an efficacy of approximately 90% in studies lasting longer than 20 weeks[20]. A systematic review of low-dose isotretinoin treatment found that the treatment response was comparable to that of the standard dose, with fewer side effects, and was more cost-effective. In addition,

Table 1. Demographic and clinical charactheristics of study groups

		Dapson plus isotretinoin n=34 Mean (SD)/n (%)	Nadifloxacin plus isotretinoin n=40 Mean (SD)/n (%)	p-value
Age		22,03 (±0.84)	24,13 (±0.72)	0,037*
Gender	Female	24 (70.6%)	21(52.5%)	0.112
	Male	10 (29.4%)	19(47.5%)	
Previous isotretinoin treatment history		3 (8.8%)	4 (10%)	0.863
Baseline disease severity (GAAS)	Moderate	11 (32.4%)	16 (40%)	0.496
	Severe	23 (67.6%)	24 (60%)	
Treatment characteristics	Time to lesion clerance	2,68 (±0.18)	3,43 (±0.15)	0.000*
	Total treatment duration (month)	5,15 (±0.14)	5,8 (±1.9)	0.009*
	Cumulative isotretinoin dosage (mg)	3376,5 (±71.9)	4155 (±88.4)	0.000*
	Dryness	10 (29.4%)	5 (12.5%)	0.071

n: Number, SD: Standard deviation, *p<0.05, statistically significant, GAAS: Global Acne Assessment Scale

combining low-dose treatment with adjuvant treatments has been suggested to improve the efficacy of treatment. However, data on the combination of oral isotretinoin with topical treatments are inadequate[3]. The combination of topical clindamycin and low-dose isotretinoin resulted in a clinical response rate of 87.6% after 6 months of treatment in patients with moderate acne[12]. In contrast, in a study comparing the efficacy of dapsone 5% gel with placebo in patients with moderate to severe acne treated with isotretinoin 20 mg/day, the reduction in the number of lesions was found to be more significant in the dapsone group, although no significant difference was found in terms of GAAS scores at week 12[5]. The study also indicated that female patients in the dapsone group exhibited a superior response compared to male patients in the same group[5], in line with the findings by Tanghetti et al.[14]. Despite increasing treatment efficacy by addition of nadifloxacin to topical retinoid, there is a lack of data evaluating the efficacy of combining nadifloxacin with oral isotretinoin[19].

Post-treatment relapse is a major clinical issue in acne treatment.

Although some studies have shown that the relapse rate after isotretinoin treatment with higher daily and/or cumulative doses is lower than that after low-dose treatment protocols, data on the frequency of relapse after treatment are conflicting. One study that followed patients for 4 years after treatment with 20 mg/day of isotretinoin found relapse rates of 3.9-5.9% and an association between relapse and polycystic ovary syndrome[21]. A review by Sardana and Garg[22] found no statistically significant difference in relapse rates between low-dose and standard-dose isotretinoin treatment for mild-to-moderate acne (34.6% vs. 21.5%). In one study, where patients with moderate acne were treated with a combination of low-dose isotretinoin and topical clindamycin, the relapse rate at six months after treatment was 16.4%[12]. In another study, patients with severe acne who were treated with a combination of oral azithromycin and low-dose isotretinoin had a relapse rate of 11.3% at 1 year after treatment, which was lower than that in many previous studies, suggesting that the combination may reduce the risk of relapse. However, further research is needed to determine the optimal combination that effectively reduces post-treatment relapses[10].

Independent risk factors for acne recurrence after isotretinoin treatment were reported to be family history, truncal acne, prepubertal acne, and the presence of inflammatory lesions at the end of treatment, rather than the cumulative dose of isotretinoin. Accordingly, to prevent recurrence, it is recommended to continue isotretinoin treatment for an additional two months after complete resolution of acne, instead of reaching the cumulative target dose[23]. However, oral isotretinoin treatment is often associated with side effects. Although side effects other than teratogenicity are typically dose-dependent, mild, and transient, they can adversely affect patient comfort and compliance. In addition, 3.2% of patients reported severe side effects that required discontinuation of treatment[20]. Therefore, it is recommended to use the lowest possible dose of isotretinoin while maintaining efficacy and without increasing the relapse rate[24]. Although combining topical treatments with low-dose isotretinoin appears to be a reasonable approach for accelerating lesion clearance and, consequently, shortening the overall duration of treatment[10], a recent study by Lai and Barbieri[25] found that a higher cumulative dosage may decrease the risk of acne relapse and the necessity for isotretinoin retreatment.

In our study, the dapsone combination seemed to reduce the treatment time for clearing acne lesions better than the nadifloxacin combination and reduced the cumulative dose of isotretinoin. However, due to the lack of post-treatment follow-up, there is no comparison between the two treatments in terms of recurrence.

Dryness is a commonly reported side effect of dapsone gel and was observed in our study with a frequency similar to that reported in the literature[5,15]. Nadifloxacin, being in cream form, generally causes less frequent dryness and irritation, and its combination with other topical treatments has been reported not to increase irritation[18,26]. Although not statistically significant in our study, dryness was observed more frequently in the dapsone group. This finding may be attributable to the supplementary moisturizing effect of nadifloxacin cream; however, it must be noted that the study did not assess several factors that influence dryness, including the daily doses of isotretinoin per body weight and the concurrent use of moisturizing creams.

Study Limitations

This study has several limitations, including its retrospective design, lack of isotretinoin monotherapy control, and lack of post-treatment follow-up.

Conclusion

Our findings suggest that topical dapsone gel may be an effective adjuvant treatment with low-dose isotretinoin to accelerate the treatment response. However, larger prospective studies are needed to identify optimal adjuvant treatment options for low-dose isotretinoin that could reduce the dose of isotretinoin and possibly the relapse rate.

Ethics

Ethics Committee Approval: This study was approved by the Acıbadem University and Acıbadem Health Institutions Medical Research Ethics Committee (ATADEK) with decision number 2024-1/26, date: 25.01.2024.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.Ö., G.E., Concept: Z.Ö., Design: Z.Ö., G.E., Data Collection or Processing: Z.Ö., G.E., Analysis or Interpretation: Z.Ö., Literature Search: Z.Ö., Writing: Z.Ö., G.E.

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