

Maintenance Treatment With Topical Adapelene in Patients With Nodulo Cystic Acne After Systemic Isotretinoin Therapy

Nodulokistik Akne İçin Sistemik İso tretinoin Kullanan Hastalarda Topikal Adapelene İle İdame Tedavisi Uygulanması

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Aim: Oral isotretinoin is a mainstay for the treatment of acne however, approximately 20% to 40% of patients require a repeated course due to recurrences.

The aim of this study was to assess the efficacy of %0.1 adapelene gel following the discontinuation of systemic isotretinoin treatment for the prevention of recurrences in patients with severe facial acne.

Patients and Methods: Thirty patients with facial nodulocystic acne used systemic isotretinoin and after the discontinuation of treatment they are instructed to use %0.1 adapelene gel every night. They were followed every 6 months for a total period of 18 months.

Results and Conclusion: Only twelve patients could manage to use %0.1 adapelene gel, two patients were missing during controls and the rest could not tolerate the treatment. None of these twelve patients had any recurrences at the end of 18 months.

Although patient tolerance may be quite low, recurrences may be fewer after isotretinoin treatment when patients are persuaded to use %0.1 adapelene gel. Controlled studies with more patients in different age groups are required to confirm these findings.

Key Words: *acne, maintenance, treatment, adapelene, isotretinoin*

Amaç: Sistemik isotretinoin akne tedavisinde etkinliği gösterilmiş bir ajandır. Bununla birlikte isotretinoin kullanan hastaların %20-40'ında tedavi sonrası rekkürens gelişmekte ve ikinci bir kür isotretinoin kullanımı gerekmektedir. Bu çalışmanın amacı sistemik isotretinoin tedavisini takiben uygulanacak %0.1 adapelene jelin rekkürensları azaltmak amacıyla etkinliğinin değerlendirilmesidir.

Hastalar ve Yöntem: Bu amaçla yüz bölgesinde nodulokistik aknesi olup sistemik isotretinoin kullanan 30 hasta çalışmaya alınmış ve sistemik tedavi sonrası topikal %0.1 adapelene jel kullanımına devam etmeleri önerilmiştir. Hastalar 6 ayda bir toplam 18 ay süre ile takip edilmişlerdir.

Bulgular ve Tartışma: Otuz hastanın sadece onikisi %0.1 adapelene jel kullanımını tolere edebilmiştir. Bu 12 hastanın hiçbirinde 18 ay sonunda akneye ait rekkürens bulgusuna rastlanmamıştır. Sistemik isotretinoin tedavisi sonrası rekkürensları azaltmak amacıyla %0.1 adapelene jel kullanımının etkinliğinin değerlendirilmesi amacıyla daha büyük ve çeşitli hasta gruplarıyla yeni çalışmalara ihtiyaç vardır. Bununla beraber hasta uyumunun düşük olabileceği de akılda tutulmalıdır.

Anahtar Sözcükler: *akne, idame, tedavi, adapelene, isotretinoin*

Acne vulgaris is the most common dermatologic disorder which can persist until the adult ages. The disease is physically and psychologically scarring and sufferers often have significantly impaired psychosocial development, reduced self-esteem and emotional distress. Thus effective treatment to

reduce the severity and potential for recurrence is extremely important for which sometimes combination therapies are indicated (1).

Oral isotretinoin is a mainstay for the treatment of especially severe cases of acne and a single course of treatment will usually clear the

Received: 19.03.2007 • Accepted: 23.08.2007

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lesions. However approximately 20% to 40% of patients require a second or repeat course due to recurrences.

Previous studies have shown that a higher relapse rate occurred in patients who received a dose of 0.5 mg/kg/body weight, or a cumulative dose less than 100-120 mg/kg/body weight. Younger age, presence of severe acne, presence of family history and a prolonged history of acne are all reported to be risk factors for recurrence (2,3,4).

After the cessation of the oral treatment usually patients are not warned about wearing oily make up and foundation, or avoiding oily and sticky sun protection creams. These warnings together with applying comedolytic topical agents to keep the pores open might prevent the recurrences in patients with severe facial acne.

The aim of this study was to assess the efficacy of %0.1 adapelene gel following the discontinuation of systemic isotretinoin treatment for preventing the recurrences in patients with severe facial acne.

Patients and Methods

Patient selection criteria for this prospective study were;

1. Patients having stable nodulocystic acne, more than 5 nodulocystic lesions on the face stage 5 or more according to Burke and Cunliffe classification (3),
2. Patients not having truncal acne,
3. Patients with a positive family history of acne either on father or mother side or both,

4. Patients who did not use isotretinoin before,

5. Female patients with normal FSH, LH, free testosterone, DHEA-S, 17 hydroxy progesterone, androstenedione and prolactin levels and with no signs of hirsutismus on face, breasts, abdomen and thighs

Thirty patients were selected according to these criteria and prescribed systemic isotretinoin at a daily dose of 0.5 mg/kg/day. They continued systemic isotretinoin until they reached a total dose of 120 mg/kg which took 8 months of treatment. Meanwhile all patients were given an oil in water, light moisturizer to use after each washing. They were also prescribed a non drying cleansing gel and a watery, spray formula for sun protection for facial use. Female patients were advised to use powder forms for make up.

During the systemic treatment they used their moisturizer after each washing and two or three more times whenever they felt dry. They used it in very small amounts like the size of three peas for the entire face.

Two months before the cessation of the systemic therapy, they are all prescribed 0.1% adapelene gel. They are told to use the gel every other night for the first two months, before going to bed, keeping the amount very small as the size of one or two peas for the entire face. It is applied at least one hour after washing and applying a moisturizer to the face.

After the discontinuation of isotretinoin, %0.1 adapelene gel was applied every night keeping the same amount. Patients never changed their moisturizers, or the amount they applied, the only difference

was they applied it only after each washing. They continued using the same sun protection spray and non comedogenic make up products.

Recurrence of acne was defined as at least five papular or nodular lesions at a time, a second course of isotretinoin was started in patients with repeating papules or nodules unresponsive to topical treatments for at least two months.

Patients were followed every 6 months, after the cessation of systemic isotretinoin unless they had problems.

Results

Patients were aged between 16-37, with an average of 26.32 ± 3.96 years. Twenty six were female and four were male. None of the female patients became pregnant during or within four weeks after the treatment.

All patients came to follow up and used systemic isotretinoin until the end of 8 months. At the end of the systemic treatment, none of the patients had any inflammatory or nodular lesions. Retentional lesions were not counted as patients would continue using a comedolytic topical agent.

However only twelve female patients could tolerate using %0.1 adapelene gel and continued using it for 18 months after the treatment. Average age of the patients (26.94 ± 4.90 vs. 26.10 ± 3.78) and average duration of acne (7.33 ± 3.38 vs. 5.50 ± 1.90) were similar in adapelene using and intolerant groups ($p = 0.96$ vs $p = 0.15$, Mann-Whitney U test) .

Two patients moved to another city

and the remaining 16 patients, although could not tolerate adapelene gel, kept coming to follow up. Patients who could not tolerate using adapelene gel had repeated attacks of irritation of the skin although they used it after the moisturizer and in very minute amounts. Once they had irritation they stopped the treatment until redness completely subsided. Afterwards they restarted using adapelene gel first every other night and if no irritation occurs every night after the first month. If they had 3 or more repeating attacks of irritation they discontinued the treatment.

At the end of 18 months, 12 patients who could tolerate using %0.1 adapelene gel did not have any recurrences of acne. On the other hand, 4 of the 16 patients (%25) who could not use %0.1 adapelene gel needed a second course of systemic isotretinoin. Although number of patients is limited, number of recurrent cases were statistically more in adapelene intolerant group ($p < 0.5$, fisher's exact test). Three of the recurrent cases were female and hormonal abnormalities were ruled out by blood tests for the second time.

Discussion

Although the effectiveness of isotretinoin against acne is undeniable, the maintenance of effect after treatment is a problem. In the past it has been shown that lower daily doses like 0.5 mg/kg or a total dose less than 120 mg/kg of isotretinoin could be related with higher relapse rates (4). It was also shown that beginning isotretinoin treatment with lower daily doses like 0.5 mg/kg might minimize some adverse effects like dry mucosa, myalgia and initial flares of acne (5). In a more recent study

lower daily doses were not shown to be a risk factor for recurrence of acne (6,7). Our patients used 0.5mg/kg/day of isotretinoin for 8 months and we did not have any acute flares or serious side effects, besides, they all responded to treatment. Although it took 8 months to receive it, all patients had a total dose of 120mg/kg. The patient selection criteria was to standardize the patient group and to have a group of patients who were likely to have recurrences like positive family history and acne with higher grade but except for hyperandrogenic states for female patients in whom systemic cyproterone acetat is suggested as the treatment of choice (6,7).

Patients with acne try many over the counter cosmetic products although they usually don't know much about them and which ones to choose to keep their pores open. Applying heavy make up with oily products or using oily sunscreens can aggravate the recurrences. One of our aims was to instruct the patients on choosing right products for moisturizing, sun protection and make up. We also wanted them to use a comedolytic agent to clear any retentional lesions, if present, and to keep their pores open to have a lasting effect of isotretinoin.

As a maintenance treatment our choice was 0.01% adapelene gel as it was shown to have a rapid onset of action and a particularly favorable tolerability profile compared with other retinoids (8). It has shown to have a similar activity in inhibiting epithelial cell proliferation to tretinoin and topical application is thought to modulate keratinisation, inflammation and differentiation of follicular epithelial cells. As a result a reduction in the formation of both microcomedones and inflammatory lesions is

detected (8). Adapelene has been found to be effective as an adjunctive treatment to topical clindamycin, oral antimicrobial medications and benzoyl peroxide in the treatment of acne.

Although tolerability of adapelene is reported to be better than other retinoids, our results showed that only twelve patients out of thirty could tolerate using it. It may be because they started using it after a long treatment with systemic isotretinoin. As a result, although they used it initially every other night, in very small amounts and always after a moisturizer, because of severe and repeating attacks of irritation most of the patients stopped using it.

A very recently published study showed the risk factors for relapse after systemic isotretinoin as severe seborrhea after treatment, high number of superficial inflammatory lesions after treatment, young age when treatment was initiated or when acne was diagnosed, family history, prepubertal acne and acne on both face and body (6).

In our study we applied the regimen to only facial acne patients. At the end of the treatment none of our patients had any inflammatory lesions left or had they prominent seborrhea. We had only two patients younger than 20 years, one of whom applied adapelene gel and has no recurrence. As for family history all of our patients had a positive family history where uncles, aunts and cousins are also considered but unlike some recent studies we did not define subgroups for family history whether from mother's or father's side or both (7).

We followed patients for 18 months after the treatment although longer follow up time may be better

for more reliable results, in previous studies, relapses were reported to be mostly during the first 2 years after discontinuation of isotretinoin (9).

Acne and cosmetic products seem to be interacting. Cosmetics that are appropriate for use in patients with acne must be noncomedogenic, nonacnegenic, nonirritating and hypoallergenic (10). Otherwise patients can have aggravation of symptoms while using some over the counter products, this is why dermatologists should be guiding

patients in selection of cosmetic products (11).

In our results out of 30 patients we had only 12 patients using adapelene gel as a maintenance treatment at the end of 18 months. In previous studies as well, patient adherence to maintenance programs were shown to be difficult and patients are advised to be motivated for treatment (12).

As a result, tolerability of adapelene gel seems to be quite low, on the other hand, adapelene gel

using group had no relapses of inflammatory acne lesions for 18 months. Although number of patients is limited, recurrences may be fewer after isotretinoin treatment when patients are warned to avoid certain cosmetic products and persuaded to use comedolytic topical agents routinely.

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