Case Report
Olgu Sunumu

DOI: 10.4274/turkderm.galenos.2019.13845
Turkderm - Turk Arch Dermatol Venereol 2020;54:19-21

Treatment of tuberous sclerosis facial angiofibromas with erbium-yttrium aluminium garnet laser and topical sirolimus 0.25%

Tüberoskleroz yüz anjiyofibromlarının erbium-itriyum alüminyum garnet lazer ve topikal sirolimus %0,25 ile tedavisi

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Abstract

Although the efficacy of topical sirolimus for facial angiofibromas of tuberosclerosis is now appreciated, drug-induced irrritation complicates the use of the concentration recommended in the literature as 1%. Adjuvant vascular or ablative laser applications may be preferred in adult patients for a variety of purposes, such as treatment of large lesions that tend to be resistant to topical treatment, reduction of topical product concentration and rapid response generation. Herein, we aimed to share the 2-year follow up result of a tuberoussclerosis case where angiofibromas were observed on the chin, malar regions and nose. We combined the full-field erbium-yttrium aluminium garnet laser application with topical sirolimus 0.25% cream on the second month of treatment.
Keywords: Erbium-YAG laser, sirolimus, mTOR inhibitor, angiofibroma

Öz

Tüberosklerozun yüz yerleşimli anjiyofibromlarında topikal sirolimusun etkinliği artık iyi bilinmekle birlikte ilaca bağlı irritasyon literatürde önerilen %1 konsantrasyonun kullanımını zorlaştırmaktadır. Adjüvan vasküler veya ablatif lazer uygulamaları, topikal tedaviye dirençli olma eğilimi gösteren büyük lezyonların tedavisi, kullanılan topikal ürün derişiminin azaltılması ve hızlı yanıt eldesi gibi çeşitli amaçlar için erişkin hastalarda tercih edilebilir. Biz burada çene, burun, malar bölgelerde yaygın yerleşimli anjiyofibroma lezyonları izlenen bir tüberoskleroz olgumuzun 2 yıllık takip sonucunu paylaşmayı amaçladık. Bu olgunun yönetiminde tüm-saha erbium-itriyum alüminyum garnet lazer uygulamasını, tedavi sonrası ikinci ayda %0,25 dozda topikal sirolimus kullanımı ile kombine ettik.
Anahtar Kelimeler: Erbium-YAG lazer, sirolimus, mTOR inhibitörü, anjiyofibrom

Introduction

Tuberous sclerosis (TS) is characterized by hamartomatous lesions of the skin and other tissues. The frequency of facial angiofibromas (FA) (adenoma sebaceum) is reported as 70-80% and these lesions have a negative impact on the quality of life due to stigmatization. Different surgical approaches including cryotherapy, electrocauterization, radiofrequency, laser treatments, dermabrasion, shave excision and curettage are tried in an effort to treat FA. In addition to the variable efficacy and the complications related to these procedures, the relapses also make the management of FA challenging. The discoveries on the role of mTOR (mammalian target of rapamycin) pathway in TS were translated to the clinical setting as the preference of topical and systemic mTOR inhibitors for the treatment of skin and nervous system involvement. The topical mTOR inhibitor treatment of FA is impressive; still, the ideal concentration, vehicle of the drug and the frequency of applications is not certain[1,2]. Herein,

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Received/Geliş Tarihi: 13.01.2019 **Accepted/Kabul Tarihi:**24.07.2019
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we report the 2-year treatment result of a TS patient managed by a combination of ablative laser and medical therapy.

Case Report

A 37-year old female with an established diagnosis of TS demonstrated bilateral symmetrical skin-coloured to erythematous infiltrated papules on bilateral malar, nasolabial regions, dorsum of the nose and the chin on admission (Figure 1). The patient was introduced, full-field erbium: Yttrium aluminum garnet laser (YAG) (Fotona, XR, Dynamis) treatment and after an informed consent pre-treatment images were captured, all widespread facial lesions were treated in the same session under fentanyl/midasolam sedation analgesia by the protection of eyes with a metal goggle. The application was performed with 100 μsn pulse duration, 10 Hz frequency and influencies between 6-10 J/cm^2 depending on the size of the papules. The treatment was continued as multiple passes till the pin-point bleeding was evident. There is not a clear consensus on the requirement of routine prophylactic antibiotherapy before full-field ablative laser applications, still especially the use of antibiotics covering gram (+) spectrum is recommended[3]. In our patient, we preferred intravenous sefazoline before laser treatment and continued therapy for one week. Topical mupirosine was applied onto the skin and the patient was followed up with bandages for one week. On 1st week control, total epithelization was detected (Figure 2). Topical mTOR inhibitor sirolimus was added to the treatment regimen of this patient due to the presence of relapsing lesions on 2nd month control (Figure 3). As topical sirolimus is not available in the market, the formulation was prepared by our faculty of pharmacy, department of pharmaceutical technology using 1 mg/mL oral solution of sirolimus (Rapamune®, Pfizer) and sufficient quantity of standard hydrophilic ointment (methylparaben 0.25 g, propylparaben 0.15 g, sodium lauryl sulfate 10 g, propylene glycol 120 g, stearyl alcohol 250 g, white petrolatum 250 g, purified water 370 g) (United States Pharmacopecia, Rockville, Maryland) to obtain sirolimus lotion. The initial dose was determined as 1% that was applied once daily. Due to the severe irritation related to this regimen, a fourfold dilution was performed and 0.25% sirolimus was better tolerated by the patient. On 3rd month control of topical sirolimus treatment, the resolution of all FA was noteworthy. On 2-year follow up period, the cessation of topical therapy was tried several times; whereas it was necessary to re-introduce the treatment due to relapses. These relapses were mild when compared to the pre-treatment lesions and a new full-field laser application was not found necessary. Still, the patient is under follow up with topical 0.25% sirolimus treatment applied thrice/week (Figure 4).

Figure 1. Pre-treatment clinical image of FA

Figure 2. Clinical image: 1st week control of full-field erbium:Yttrium aluminium garnet laser laser treatment

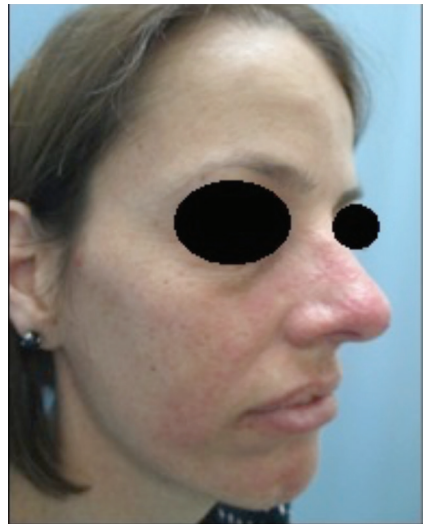

Figure 3. Clinical image: On the 2nd month control of laser application, a tendency for recurrence was detected

Discussion

The first laser application of FA is reported in 1988 with argon laser and the recurrence rates were high on long term follow-up[4]. Currently, lasers to treat FA can be mainly classified as ablative and vascular lasers. As ablative lasers, carbondioxide (CO_2) and erbium:YAG lasers are preferred to flatten the raised lesions; whereas as vascular lasers, pulsed-dye laser and nd:YAG laser are efficient for the alleviation of excess vascularization; hence the erythema component. Similar to the first reports, recurrence is common after different laser modalities, whereas the patients commonly describe a milder disease course when compared to their pre-treatment condition[5].

Topical mTOR inhibitors serve as targeted treatment agents for TS regarding the role of Pi3K-AKT-mTOR pathway in the etiopathogenesis. The promising results from case reports were confirmed in large-scale

Figure 4. Clinical image: 2nd year follow up result of sirolimus 0.25%

prospective studies. In 2017, "Treatment" trial compared the efficacy of two different concentrations (0.1%, 1%) of topical sirolimus with placebo and 1% sirolimus was found to be superior[6]. However, as in our patient, significant irritation with topical sirolimus significantly impairs patient compliance for 1% sirolimus treatment. Current data on the efficacy of topical sirolimus for FA indicate that especially large lesions tend to be resistant. Data on the combination of topical sirolimus with laser treatments are limited and in a case report, a 26-year-old female patient received electrocauterization, pulsed-dye laser and fractional CO_2 laser combination followed by 0.2% topical sirolimus treatment twice a day[7]. Park et al.[8] also combined CO_2 laser with 0.2% topical sirolimus twice a day and during maintenance period the treatment was adjusted to 0.1% concentration applied thrice per week.

More recently, in a case report, 0.05% topical sirolimus treatment was administered twice a day for 5 months, followed by a one-session combination of sequential fractional CO_2 laser, 1064 nm nd:YAG laser and 595-nm pulsed dye laser treatment. Topical sirolimus treatment was continued after the laser combination. In regard to the beneficial outcome of this combination, the authors concluded that the combination of laser treatments with topical sirolimus at much lower concentrations might be a rational alternative for larger lesions[9].

The thermal damage accompanying ablation depth is much lower with erbium:YAG laser when compared to CO_2 laser. Throughout our literature research, the data on the efficacy of erbium:YAG laser for FA was limited to a series including 13 TS patients treated with a combination of erbium: YAG laser, CO_2 laser and pulsed dye laser[10].

However, our case connotes the safety of erbium:YAG laser providing precise controlled ablation without scatrization and dyspigmentation. The combination with topical sirolimus resulted in favorable treatment results. Additionally, although we did not use a vascular laser, a significant response in erythema component except the tip of the nose suggests that the efficacy of sirolimus against vascular proliferation can be sufficient for most lesions, and it might be reasonable to evaluate the need for a vascular laser after 3-4 months of topical treatment.

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.B., E.Ç., K.K., İ.G., C.K.Ö., Concept: A.B., E.Ç., İ.G., Design: A.B., E.Ç., İ.G., Data Collection or Processing: A.B., E.Ç., K.K., İ.G., Analysis or Interpretation: A.B., E.Ç., K.K., İ.G., Literature Search: A.B., E.Ç., İ.G., C.K.Ö., Writing: A.B., E.Ç., K.K., İ.G., C.K.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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