Research article

mucosa

DOI: 10.33204/mucosa.1089760

Effects of systemic isotretinoin treatment on retinal nerve fiber layer thickness and corneal endothelial cell density

Sistemik izotretionin tedavisinin retina sinir lifi tabakası kalınlığı ve kornea endotel hücre yoğunluğu üzerindeki etkileri

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Abstract

Objective To investigate the effects of systemic isotretinoin therapy on retinal nerve fiber layer (RNFL) thickness and corneal endothelial cell density (ECD)

Methods Thirty-three patients completed the study. All patients were given an ophthalmic examination at baseline and after six months of isotretinoin therapy. All patients underwent a detailed eye examination including best corrected visual acuity, intraocular pressure, refractive errors, biomicroscopic anterior segment and fundus examination. In addition, Schirmer test without topical anesthesia, tear break up time, retinal nerve fiber thickness measurements with optical coherence tomography (OCT) and specular microscopy measurements were performed on all patients.

Results There were 23 female (69.7 %) and 10 male (30.3 %) patients. Post treatment RNFL values were significantly lower than pretreatment values on both right and left eyes (P=0.048 and P<0.001). We did not find any correlation between total dose of isotretinoin and mean RNFL thickness values on both right and left eyes (P=0.118, P=0.909). There were no significant differences in the mean Schirmer scores, Break up time values of both eyes during the treatment compared with the baseline values. There were significant differences in corneal ECD between pre and postreatment period (P=0.017, P=0.006).

Conclusion After the use of oral isotretinoin for six months, we found decreased RNFL and CCT thickness by OCT.

Key words: *isotretinoin, eye, cornea, retina*

Öz

Amaç Sistemik izotretinoin tedavisinin retina sinir lifi tabakası (RSLT) kalınlığı ve kornea endotel hücre yoğunluğu

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Received: 28 March 20221 ***Accepted:*** 30 May 2022
Conflicts of Interest: None
Funding: None
How to cite this article: Uzlu D, Baykal Selcuk L, Turk A, Oguzer SE, Ozbay AD, Yasar Y. Effects of systemic isotretinoin treatment on retinal nerve fiber layer thickness and corneal endothelial cell density. Mucosa 2022;1:13-19.

üzerindeki etkilerini değerlendirmek.

Yöntem Otuz üç hasta çalışmayı tamamladı. Tüm hastalara başlangıçta ve tedavi süresince tedavinin başlangıcından altı ay sonra oftalmik muayene yapıldı. Tüm hastalara düzeltilmiş görme keskinliği, göz içi basıncı, kırma kusurları, biyomikroskopik ön segment ve fundus muayenesini içeren detaylı bir göz muayenesi yapıldı. Ayrıca tüm hastalara topikal anestezi yapılmadan Schirmer testi, gözyaşı kırılma zamanı bakıldı, optik koherens tomografi ile retina sinir lifi kalınlık ölçümleri ve speküler mikroskopi ölçümleri yapıldı.

Bulgular 23 kadın (%69.7) ve 10 erkek (%30.3) hasta dahil edildi. Tedavi sonrası RSLT kalınlığı hem sağ hem de sol gözde tedavi öncesi değerlerden anlamlı derecede düşüktü (P=0.048 ve P<0.001). Hem sağ hem de sol gözde toplam izotretinoin dozu ile ortalama RSLT kalınlık değerleri arasında herhangi bir ilişki bulunamadı (P=0.118, P=0.909). Tedavi sırasında her iki gözün ortalama Schirmer skorları, kırılma zamanı değerlerinde başlangıç değerleriyle karşılaştırıldığında anlamlı bir fark yoktu. Kornea endotel hücre yoğunluğunda tedavi öncesi ve sonrası dönem arasında anlamlı farklılıklar vardı (P=0.017, P=0.006).

Sonuç Altı ay süreyle oral izotretinoin kullanımı sonrası OKT ile RSLT ve kornea kalınlığında azalma saptadık.

Anahtar kelimeler: *izotretinoin, göz, kornea, retina*

Introduction

Oral isotretinoin was approved by the FDA in 1982 for the treatment of severe acne. It is the first-line treatment choice in severe acne vulgaris. Isotretinoin is the only drug that can be effective on all the factors that are valid in acne vulgaris pathogenesis.[1]

There are many side-effects of oral isotretinoin treatment, most commonly dose-dependent side-effects include cheilitis, dermatitis, facial erythema, xerosis, mucositis, epistaxis, conjunctivitis and blepharitis; the majority of these can be predicted and do not require treatment termination.[1] The majority of ocular side-effects are meibomian gland atrophy, impaired meibomian gland secretion, blepharoconjunctivitis, dry eye, keratitis, myopia, decreased color vision, optic neuritis, diplopia, optic disc edema and idiopathic intracranial hipertansiyon.[2,3] In a retrospective study Brzesinski et al., showed that the frequency of ocular side effects was 8.96% and the most common side effect was dry eye disease (5.7%) in 3525 patients who received isotretinoin treatment (0.2-0.5 mg/kg/day).[4]

Good visual acuity requires a transparent cornea which is essential for the formation of a clear image on the retina. The corneal endothelium has both barrier and pump functions, which are important for the maintenance of corneal clarity. The RNFL of the retina contains the non-myelinated axons of the retinal ganglion cells that form the optic nerve. The measurement of retinal nerve fiber layer (RNFL) thickness is a valuable tool for demonstrating early retinal damage.[4,5]

Recently with the introduction of optical coherence tomography devices, noninvasive and objective imaging has been used frequently. In a study Ucak et al. determined that there was focal thinning in the retinal nerve fiber layer in patients using isotretinoin.[5] Sekeryapan et al. reported that there was no change in the nerve fiber layer and ganglion cell layer in 28 patients using isotretinoin.[6] Although some of the side effects associated with the use of isotretinoin are well established, there are not many publications in the literature on changes and damage in the anatomical structures of the eye.

In this study, we aimed to contribute to the literature by evaluating retinal nerve fiber thickness and corneal endothelial cell density changes that may develop in the eye due to isotretinoin treatment.

Methods

Fifty patients with acne vulgaris were enrolled into this observational study. Patients' pretreatment demographic and clinical characteristics (age, gender, follow-up time, total dose of isotretinoin) were recorded. All of the patients were treated for acne with

systemic isotretinoin in total dosages of at least 0.3-0.5 mg/kg /day for a period of six months. Thirty-three patients completed the study.

All patients were given an ophthalmic examination at baseline and during the treatment, six months of the start of the treatment. All patients underwent a detailed eye examination including best corrected visual acuity, intraocular pressure, refractive errors, biomicroscopic anterior segment and fundus examination. In addition, Schirmer test without topical anesthesia, tear breakup time, retinal nerve fiber thickness measurements with optical coherence tomography and specular microscopy measurements were performed on all patients.

The study was approved by the Local Ethics Committee of Karadeniz Techinical University School of Medicine and has been conducted in accordance with the guidelines for human studies and Declaration of Helsinki. Informed consent was obtained from all subjects.

High myopia or hyperopia (>6.00 D), corneal astigmatism >2.5 D, axial length greater than 26 mm and shorter than 22 mm, any known ocular disease (glaucoma, ocular hypertension, uveitis, cornea pathology), a history of ocular surgery, a history of contact lens use, and those who could not comply with any of the measurement methods were not included in the study. Intraocular pressure measurements were made with a non-contact tonometer device (Nidek NT-530, Japan). Schirmer test was performed without applying topical anesthesia to the patient. Filter papers (Whatman filter paper, Optitect) measuring 5x35 mm were placed in the conjunctival fornix on the outer 1/3 of the patient's lower lid. The patient was asked to blink as necessary and close the eye. After five minutes, the amount of wetness was measured and evaluated. Values below 10 mm were evaluated in favor of aqueous tear insufficiency.

To measure the tear breakup time (BUT), fluorescein drops were instilled into the lower fornix without the use of topical anesthetics. Fluorescein was spread by asking the patient to blink 3-4 times. The tear film was examined in a slit-lamp microscope with wide illumination using a cobalt blue filter. The time from the last blink to the first dry spot was determined. The measurement was repeated three times and averaged, and the measurement of this value below ten seconds was considered pathological.

Specular microscopy was performed with the non-contact specular microscopic measurement NIDEK (CEM-530) device. While measuring, it was noted that the highest quality image was obtained. With the measurement, endothelial cell density (ECD), central corneal thickness (CCT) were calculated. OCT measurements were made with the Optovue RTVue (RT 100, software version 6.3, Optovue, Fremont, CA) device. Peripapillary RNFL was placed on the optic disc head with a 3.4 mm scanning diameter ring around it and mean inferior, superior, nasal and temporal thickness measurements were made. All measurements were made by the same technician.

Statistical analysis

Data analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). The normality of the data was confirmed using a Kolmogorov-Smirnov test. A paired t test was used to compare the study measurements at the baseline and at follow-up visits. Mann Whitney U test was performed for non-normally distrubited data. The correlation analysis between the mean RNFL score, the total dose of isotretinoin were analysed using Pearson's correlation tests. Differences with a value of $P<0.05$ were considered to be statistically significant.

Results

Demographic data

There were 23 female (69.7 %) and 10 male (30.3 %) patients. Mean age was 19.80 ± 5.70 years, with a range of 13-44 years. The mean daily dosage of isotretinoin was 29.09 ± 6.10 mg, mean follow up time of the drug use was 6.36 ± 0.80 months. The total dose of isotretinoin was 7345 ± 1084 (5400-9000) mg. The severity of acne was moderate in 16 patients (48.5%) and severe in 17 (51.5%).

Differences between the baseline and during the treatment

The relationship between ocular changes in all eyes at the baseline and during the treatment is summarized in Table 1.

Before and after treatment, a complete ophthalmologic examination was normal in all eyes.

There were no significant differences in the mean Schirmer scores, BUT values of both eyes during the treatment were compared with the baseline values. Post treatment RNFL values were significantly lower than pretreatment values on both right and left eyes ($P = 0.048$ and $P<0.001$). We did not find any correlation between total dose of isotretinoin and RNFL values on both right and left eyes ($P=0.118$, $P=0.909$).

The BUT values were 8.20 ± 2.80 in the right eye at the beginning of the treatment, 7.80 ± 2.40 in the 6th month of the treatment, 8.40 ± 2.80 in the left eye at the beginning of the treatment and 7.60 ± 2.20 in the 6th month of the treatment. No statistically significant

Table 1. Averages of the RNFL thickness, Corneal Endothelial Cell Density, BUT values and Schirmer test scores before and during the treatment

Tests (mean +-SD)	Baseline	Sixth month	*P* value
TO right	15.00 ± 3.30	14.30 ± 2.30	0.377
TO left	15.10 ± 2.80	14.10 ± 2.70	0.202
CD right	2768.64 ± 172.40	2683.70 ±262.94	0.125
CD left	2821.30 ± 282.70	2744.48 ±262.89	0.257
RNFL right	108.71 ± 7.470	105.08 ± 7.16	**0.048**
RNFL left	109.75 ± 9.48	101.99 ± 6.75	**<0.0001**
RNFL superior right	130.10 ± 12.42	110.00 ± 11.40	**<0.0001**
RNFL superior left	129.80 ± 20.44	113.43 ± 12.30	**0.004**
RNFL inferior right	128.60 ± 15.62	109.59 ± 9.03	**<0.0001**
RNFL inferior left	124.60 ± 13.61	108.47 ± 9.89	**<0.0001**
RNFL temporal right	81.90 ± 12.53	78.40 ± 18.43	0.581
RNFL temporal left	80.43 ± 13.98	71.40 ± 7.82	0.061
RNFL nasale left	81.23 ± 11.34	78.90 ± 18.43	0.555
RNFL nasale right	79.37 ± 18.35	75.70 ± 9.15	0.550
CCT right	591.91 ± 40.31	555.37 ± 26.41	**0.017**
CCT left	589.27 ± 36.21	553.84 ± 29.02	**0.006**
BUT right	8.20 ± 2.80	7.80 ± 2.40	0.545
BUT left	8.40 ± 2.80	7.60 ± 2.20	0.227
Schirmer right	13.10 ± 6.90	13.60 ± 6.40	0.757
Schirmer left	13.70 ± 6.90	14.20 ± 5.60	0.740

difference was observed in terms of BUT values at the beginning and end of the treatment (P>0.05). The mean Schirmer test scores in the right eye was 13.10 ± 6.90 at the beginning of the treatment, it was 13.60 ± 6.40 in the 6th month. The mean Schirmer test in the left eye was 13.70 ± 6.90 at the beginning of treatment and 14.20 ± 5.60 at the 6th month of treatment. There was no statistically significant difference in terms of Schirmer test scores at the beginning and end of the treatment (P>0.05).

While the mean corneal ECD in the right eye was 2768.64 ± 172.40 cells/mm^2 at the beginning of treatment, it was 2683.70 ± 262.94 cells/mm^2 at the 6th month of treatment. The mean corneal ECD in the left eye was 2821.30 ± 282.70 cells/mm^2, it was 2744.48 ± 262.89 cells/mm^2 at the 6th month of treatment. No statistically significant difference was observed in terms of corneal ECD at the beginning and end of the treatment (P>0.05).

The mean retinal nerve fiber thickness (RNFL) in the right eye was 108.71 ± 7.47 µm at the beginning of treatment and 105.08 ± 7.16 µm at the 6th month of treatment (P=0.048). The mean RNFL was 109.75 ± 9.48 µm in the left eye and 101.99 ± 6.75 µm at six months of treatment (P<0.0001). Superior RNFL thickness was 130.10 ± 12.42 µm at the beginning of treatment in the right eye, and 110.00 ± 11.40 µm at the 6th month of treatment (P<0.0001). Superior RNFL thickness in the left eye was 129.80 ± 20.44 µm at the beginning of treatment and 113.43 ± 12.30 µm at the 6th month of treatment (P=0.004). Inferior RNFL in the right eye was 128.60 ± 15.62 µm at the beginning of treatment and 109.59 ± 9.03 µm at the 6th month of treatment (P<0.0001). Inferior RNFL in the left eye was 124.60 ± 13.61 µm at the start of treatment and 108.47 ± 9.89 µm at six months of treatment (P<0.0001). There was no statistically significant difference in terms of temporal and nasal RNFL thickness in the right and left eyes at the beginning of treatment and at the sixth month of treatment (P>0.05).

CCT was 591.91 ± 40.31 µm in the right eye at the beginning of treatment and 555.37 ± 26.41 µm at the 6th month of treatment (P=0.017). CCT in the left eye was 589.27 ± 36.21 µm at the beginning of treatment and 553.84 ± 29.02 µm at the 6th month of treatment (P=0.006).

Discussion

Ocular side effects of systemic isotretinoin were encountered with moderate frequency. Most ocular side effects associated with oral isotretinoin use are dose dependent. Ocular side effects of isotretinoin are meibomian gland atrophy, impaired meibomian gland secretion, blepharoconjunctivitis, dry eye, keratitis, myopia, decreased color vision, optic neuritis, diplopia, optic disc edema.[2,3]

In our study, we found that mean, superior and inferior RNFL thickness decreased in both eyes at the end of the 6-month follow-up period. In the literature, studies investigating the effects of isotretinoin treatment on RNFL thickness show different results. Kapti et al.[7] found no significant difference in RNFL thickness in the 6-month follow-up of patients who received systemic isotretinoin treatment compared to pretreatment. Sekeryapan et al.[6] examined the changes in RNFL and ganglion cell complex in patients receiving 1 mg/kg/day oral isotretinoin treatment and reported that systemic isotretinoin treatment had no negative effect on RNFL thickness and ganglion cell complex. Similarly, Bakbak et al. showed that isotretinoin did not cause a statistically significant change in peripapillary RNFL thickness or visual field findings within the usage period, and within three months after cessation. Karadag et al[9] reported that after the use of oral isotretinoin for three months, no significant side effects were observed in choroidal thickness, CMT, and RNFL thickness by OCT.

Unlike these studies; Yilmaz et al.[10], observed that the RNFL thickness in the temporal quadrant was significantly lower at baseline, 1st, 2nd and 3rd months compared to baseline, and no significant change was observed in the other quadrants. Ucak et al.[5] measured RNFL subjects receiving oral 0.5-2 mg/kg/day oral isotretinoin treatment and found a thinning in the inferior temporal quadrants. In our study RNFL

thinning in the superior and inferior quadrants of both eyes were detected, however not in temporal and nasal quadrants.

Some studies have shown that systemic isotretinoin treatment has no effect on Schirmer scores.[11,12] Yildirim et al. applied Schirmer test without anesthesia and Schirmer test with topical anesthesia before treatment, at 1, 3, 6 months and 6 months after the end of treatment to 54 patients who were taking isotretinoin. There was no significant change in the Schirmer test without anesthesia, and a statistically significant decrease was observed in the Schirmer test with topical anesthesia during the treatment compared to the pretreatment.[13] In our study, no statistically significant difference was observed in the mean non-anesthetic Schirmer test measurements before the treatment and at the sixth month after the treatment.

In our study, no statistically significant difference was observed in the number of corneal endothelial cell density before and after the 6-month follow-up with systemic isotretinoin treatment. In our study, significant change was observed in CCT measurements at the 6th month of treatment compared to pre-treatment. Similarly, Yuksel et al. investigated the changes in CCT and Meibemoim gland disease score severity in 47 patients receiving systemic isotretinoin therapy.[14] A significant change was observed in CCT measurements at the 6th month of treatment compared to pre-treatment. In addition, it was determined that CCT values and the severity of Meibemoim gland disease showed a negative correlation at the 6th month of the treatment. Similarly, Cumurcu et al. reported that CCT decreased at the 6th month after systemic isotretinoin treatment compared to the pre-treatment level.[15]

Conducting the study with a small number of patients, evaluating the short-term data, the limitations of our study. More detailed information can be obtained with new studies to be carried out considering these situations. In our study, we did not examine whether the decrease in RNFL thickness and the increase in corneal thickness observed due to isotretionin use improved after drug discontinuation or not.

In conclusion our study showed that oral isotretinoin therapy could cause regional thinning in RNFL and CCT. It is necessary to monitor the patients receiving systemic isotretinoin therapy closely for adverse effects in ocular system.

Ethics committee approval: Local Ethics Committee approval was obtained.

Informed consents: They were obtained.

Peer-review: Externally peer-reviewed.

Authorship contributions:

Conception and design, or analysis and interpretation of data: DU, LBS, AT

Drafting the manuscript or revising the content: DU, LBS, AT

Final approval of the version to be published: DU, LBS, AT, SEO, ADO, YY

References

1. Ruiz-Lozano RE, Hernandez-Camarena JC, Garza-Garza LA, Bustamante-Arias A, Colorado-Zavala MF, Cardenas-de la Garza JA. Isotretinoin and the eye: A review for the dermatologist. Dermatol Ther 2020;33:e14029.
2. Egger SF, Huber-Spitzy V, Bohler K, et al. Ocular side effects associated with 13-cis-retinoic acid therapy for acne vulgaris: clinical features, alterations of tearfilm and conjunctival flora. Acta Ophthalmol Scand 1995;73:355-7.
3. Fraunfelder FT, Fraunfelder FW, Edwards R. Ocular side effects possibly associated with isotretinoin usage. Am J Ophthalmol 2001;132:299-305.
4. Brzezinski P, Borowska K, Chiriac A, Smigielski J. Adverse effects of isotretinoin: a large, retrospective review. Dermatol Ther 2017;30:2-7.
5. Ucak H, Aykut V, Ozturk S, Cicek D, Erden I, Demir B. Effect of oral isotretinoin treatment on retinal nerve fiber layer thickness. J Cutan Med Surg 2014;18:236-42.
6. Sekeryapan B, Dilek N, Oner V, Turkyilmaz K, Aslan MG. Retinal nerve fiber layer and ganglion cell layer thickness in patients receiving systemic isotretinoin therapy. Int Ophthalmol 2013;33:481-4.

7. Kapti BH, Aslan G, Yavruoglu MA. Evaluation of retinal nerve fiber layer changes with oral isotretinoin treatment. Ophthalmol Ther 2013;2:19-23.
8. Bakbak B, Gedik S, Koktekir BE, Guzel H, Altınyazar HC. Structural and functional assessment in patients treated with systemic isotretinoin using optical coherence tomography and frequency-doubling technology perimetry. Neuroophthalmology 2013;37:100-3.
9. Karadag O, Kocamaz M, Dastan M, Ozturk Durur S. Assessment of macular choroidal thickness, central macular thickness and retinal nerve fiber layer in patients receiving oral isotretinoin treatment. Cutan Ocul Toxicol 2020;39:233-6.
10. Yilmaz U, Kucuk E, Koc C, Ozkose A. Investigation of the effects of systemic isotretinoin treatment on retinal nerve fiber layer and macula. J Dermatolog Treat 2017;28:314-7.
11. Neudorfer M, Goldshtein I, Shamai-Lubovitz O, Chodick G, Dadon Y, Shalev V. Ocular adverse effects of systemic treatment with isotretinoin. Arch Dermatol 2012;148:803-8.
12. Karalezli A, Borazan M, Altinors DD, Dursun R, Kiyici H, Akova YA. Conjunctival impression cytology, ocular surface, and tear-film changes in patients treated with systemic isotretinoin. Cornea 2009;28;46-50.
13. Yildirim Y, Olcucu O, Agca A, et al. Evaluation of corneal topography and biomechanical parameters after use of systemic isotretinoin in acne vulgaris. J Ophthalmol 2014;2014:701361.
14. Yuksel N, Ozer MD, Akcay E, Ozen U, Uzun S. Reduced central corneal thickness in patients with isotretinoin treatment. Cutan Ocul Toxicol 2015;34:318-21.
15. Cumurcu T, Sener S, Ozsoy E, Doganay S. Changes in anterior chamber parameters with the pentacam rotating scheimpflug and axial length measurements by ultrasound in patients who use isotretinoin. Curr Eye Res 2012;37:395-8.