ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Changes in Ocular Surface and Corneal Epithelial Thickness with Systemic Isotretinoin Treatment

Sistemik İzotretinoin Tedavisinin Oküler Yüzey ve Kornea Epitel Kalınlığı Üzerine Etkisi

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ABSTRACT Objective: To evaluate the effect of systemic isotretinoin treatment on central corneal epithelial (CET), tear film corneal epithelial thickness(TCET) and mean central corneal thickness (CCT) measured by anterior segment optical coherence tomography (AS-OCT). **Material and Methods:** Patients who had severe nodulocystic acne disease and evaluated in our clinic prior to oral 0.5-1 mg/kg/day isotretinoin treatment were recruited. Ocular surface changes were evaluated by tear film break-up time (BUT) and Schirmer tests and ocular complaints were scored by Ocular Surface Disease Index (OSDI) questionnaire. Mean central CET, TCET and mean CCT were measured by using AS-OCT. These detailed examinations and measurements were performed prior to systemic isotretinoin intake and on the following first, third and sixth months of treatment. These data were compared statistically to find out the changes with this treatment. **Results:** Sixty four eyes of 17 female and 15 male patients were recruited. The mean age of the patients was 17.5±2.3 years. The mean CCT decreased gradually in three months (p=0.001). The mean TCET was not affected during treatment (p=0.154).The mean CET increased on the first month and decreased on the third month and increased again on the sixth month of the treatment (p=0.041, p=0.010, p=0.006). Tear film BUT decreased gradually in six months (p<0.001).The change in Schirmer test was not statistically significant (p=0.079).The OSDI scores gradually increased (p<0.001). **Conclusion:** Mean central CET and CCT measured by AS-OCT were found to be affected in the early period of oral isotretinoin treatment.

Keywords: Oral isotretinoin treatment; corneal epithelial thickness; anterior segment optical coherence tomography

ÖZET Amaç: Sistemik izotretinoin tedavisi alan hastalarda ön segment optik koherens tomografi (ÖS-OKT) ile merkezi kornea epitel kalınlığı (MKEK), gözyaşı filmi korneal epitel kalınlığı (GYKEK) ve ortalama merkezi korneal kalınlık (MKK) ölçümlerindeki değişimlerin değerlendirilmesi. **Gereç ve Yöntemler:** Şiddetli nodülokistik akne sebebiyle oral 0,5-1 mg/kg/gün izotretinoin tedavisi alacak olan hastalar değerlendirildi. Oküler şikayetler oküler yüzey hastalık indeksi (OSDI) anketi ile oküler yüzey değişiklikleri ise gözyaşı filmi kırılma zamanı (GYKZ) ve Schirmer testleri ile değerlendirildi. Ortalama MKEK, GYKEK ve MKK, ÖS-OKT ile ölçüldü. Ölçümler izotretinoin tedavisi başlangıcında, bir, üç ve altıncı ay sonunda yapılarak, zaman içindeki değişimi istatistiksel olarak analiz edildi. **Bulgular:** Onyedi kadın, 15 erkek hastanın 64 gözü çalışmaya alındı. Hastaların yaş ortalaması 17,5±2,3 idi. Ortalama MKK üçüncü ayda azaldı (p=0,001). Ortalama GYKEK tedavi sırasında etkilenmedi (p=0,154). Ortalama MKEK 1. ayda arttı, 3. ayda azaldı ve tedavinin 6. ayında tekrar arttı (p=0,041, p=0,010, p=0,006). GYKZ altı ayda yavaş yavaş azaldı (p<0,001). Schirmer testindeki değişiklik istatistiksel olarak anlamlı değildi (p=0,079). OSDI skoru kademeli olarak arttı (p<0,001). **Sonuç:** Oral izotretinoin tedavisinin erken döneminde ortalama MKEK ve MKK'ın ÖS-OKT ile yapılan ölçümlerini etkilediği görüldü.

Anahtar Kelimeler: Oral izotretinoin tedavisi; kornea epitel kalınlığı; ön segment optik koherens tomografi

Acne vulgaris is a chronic skin disorder.[1] Isotretinoin has been used for antibiotic resistant nodulocystic acne and approved by the FDA.[2] The main effect of isotretinoin is to decrease the sebaceous gland reaction. The receptors of retinoic acid exist in almost whole over the human organism, therefore isotretinoin causes so many adverse effects.[2,3] Dryness, contact lens intolerance and conjunctivitis are the side effects which have been reported commonly, regarding the eye.[2-4] Light sensitivity, failure of colour perception, distrupted night vision, optic neuritis and keratitis are other less common side effects on the eye. These effects usually clear away after cessation of the drug.[4]

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Optical coherence tomography (OCT) was applied to investigate the possible side effects of oral isetiretinoin on the retinal nerve fiber layer and ganglion cell complex, previously.[5-7] This device has been widely used for detecting many pathologies especially diseases affecting retinal layers and optic nerve in ophthalmology because it is non-invasive, non-contact, reliable and well-tolerated by patients. Anterior segment OCT (AS-OCT) has been used for ocular surface disorders, in recent years. Obtaining 'optical biopsies' of anterior segment lesions and different ocular surface are probable with this device.[8] Corneal epithelial thickness (CET) can also be measured by AS-OCT and even the tear film layer might be distinguished in high resolution AS-OCT.[9] The alterations in CET measured by AS-OCT according to dry eye disease were reported, previously.[9,10] As mentioned above, oral intake of isotretinoin might cause dry eye disease (DED) and the effects of this drug on ocular surface had been investigated by using Schiempflug based topography and meibography devices.[11-13]

The purpose of this research was to assess the changes in central corneal epithelial (CET), tear film corneal epithelial thickness (TCET) and mean central corneal thicknesses (CCT) determined by AS-OCT due to systemic isotretinoin use. Tear film break-up time (BUT), Schirmer test and ocular surface disease index (OSDI) score were also assessed as secondary objective of this study. For aught we know, this is the first research assessing the influence of systemic isotretinoin on corneal epithelial thickness measured by AS-OCT.

MATERIAL AND METHODS

This research was directed by the Ophthalmology and Dermatology Departments. First confirmation from the Institutional Review Board (71522473 /050.01.04/117) was retrieved and informed consent was taken from all patients. This research was conducted according to the Declaration of Helsinki.

Patients who had severe nodulocystic acne disease and evaluated in our clinic prior to oral 0,5-1 mg/kg/day isotretinoin treatment were recruited in the study. Patients who had the Meibomian gland disease, DED and other ocular surface diseases, previous ocular surgery were not included in this study. Besides, patients who used contact lenses within three months and especially had systemic autoimmune diseases were excluded. Complete ophthalmic evaluation, including best corrected visual acuity (BCVA), intraocular pressure (IOP) measurement by non-contact tonometer (Nidek, TONOREF II), slit-lamp biomicroscopic exam for anterior segment and fundus evaluation were made. Tear film BUT and Schirmer tests were performed. Patients were administered the OSDI questionnaire to evaluate DED-related symptoms. Then mean central CET, TCET and mean CCT were measured by using AS-OCT. This detailed examination was performed four times: prior to systemic isotretinoin intake, one month, three and six months after the initiation of treatment.

Tear film BUT was measured after a drop of 2% fluorescein was instilled. The time between the last blink and the appearance of dry spot was evaluated two times and the average value was obtained and recorded.[14]

Schirmer test was applied with a topical anesthetic agent (proparacaine HCl, Alcaine). Schirmer strips were inserted in the inferior fornix, and the patients closed their eyes for 5 minutes, then the wet part of the strip was read and noted.[14]

Cirrus enhanced depth imaging OCT (EDI-OCT, Carl Zeiss Meditec, Dublin, CA, USA) was performed to get high resolution anterior segment images. Images with signal strength of ≥8 were evaluated. The mean CCT and central CET were evaluated manually with the markers supplied by the AS-OCT software. The markers were located vertical to the ocular surface epithelium from a side just near the tear film (first hyperreflective layer) to the Bowman membrane (third hyperreflective layer) for measuring TCET and then they were placed from the second hyperreflective layer (the beginning of epithelium) to the third hyperreflective layer as Bowman membrane to measure central CET and finally the whole thickness of central cornea was measured. All measurements were performed manually by one examiner (N.Ö.A) from five varied locations of every central image and the mean value was used for statistical analysis.

Statistical analysis was applied by SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL, USA). The variables were investigated using analytical methods (Shapiro-Wilk's test) to determine whether or not they were normally distributed. Descriptive analyses were presented using mean and standart deviation for normally distributed variables. A one-way repeated measures ANOVA was conducted to compare the effect of systemic isotretinoin use on CET, TCET, CCT, tear film BUT, Schirmer test and OSDI score measurements prior to and first, third, sixth months of treatment. The significance level was evaluated as $\alpha = 0.05$.

RESULTS

Sixty four eyes of 17 female and 15 male subjects were recruited. The mean age of the patients was 17.5 ± 2.3 years. The mean BCVA measured by Snellen chart was 0.9±0.02 decimal. The mean IOP was 16.8± 2.1 mm Hg.

The results of mean central TCET, CET and CCT were summarized in Table 1.

The mean CCT decreased gradually during the initial three months of the treatment and a rise was seen on the sixth month of treatment (p= 0.001, p<0.001).

The mean TCET did not change with the treatment on the following sixth months of treatment (p= 0.154, p= 0.423).

The mean central CET increased on the first month and decreased on the third month and increased again on the sixth month of the treatment (p= 0.046, p= 0.006).

The measurements of tear film BUT, Schirmer test and OSDI score outcomes are presented in Table 2. Tear film BUT decreased gradually with isotreinoin treatment during initial six months (p= 0.001). The Schirmer test did not statistically change with treatment during six months (p= 0.191). The OSDI scores gradually increased during the initial six months (p<0.001).

Table 3 shows p values analyzed by using repeated measures of ANOVA test. According to these analyses, the mean tear film BUT was lower on the sixth month of treatment than prior to treatment. The change was mainly seen in the initial three months. The statistically significant change in the mean CCT was seen on the first month of the treatment (p= 0.004). The statistically significant alteration in the mean CET was seen in the initial three months.

TABLE 1: The mean CCT, mean TCET and the mean CET values prior to treatment, in the first, third and sixth months of isotretinoin treatment.

Months	Mean CCT (µ)	Mean TCET (µ)	Mean CET (µ)
Prior	565.7±16.4 (*p=0.128)	59.7±3.2 (*p=0.068)	47±1.8 (*p=0.101)
1 month	556.5±10.5 (*p=0.101)	60.5±3.9 (*p=0.055)	50.5±2.9 (*p=0.225)
3 months	554.5±11.6 (*p=0.125)	57±2.1 (*p=0.078)	46.5±2.3 (*p=0.168)
6 months	558.7± 14.7 (*p=0.211)	59.5±3.3 (*p=0.067)	48±2.1 (*p=0.098)

CCT: central corneal thickness; TCET: tear and corneal epithelial thickness; CET: corneal epithelial thickness.
*Shapiro-Wilk's test (Test of Normality).

TABLE 2: The mean tear film BUT, mean Schirmer test and the mean OSDI score values prior to treatment, in the first, third and sixth months of isotretinoin treatment.

Months	Tear film BUT (second)	Schirmer test (mm)	OSDI Score
Prior	23.2± 5.9 (*p=0.146)	28±7.8 (*p=0.110)	6.3±2.2 (*p=0.633)
1 month	16.5 ±5.6 (*p=0.068)	24.3 ±12.6 (*p=0.090)	9.5±3.3 (*p=0.057)
3 months	12.2±8.3 (*p=0.057)	25.6±10.6 (*p=0.055)	18.9±7.2 (*p=0.512)
6 months	8.7±7.3 (*p=0.063)	20.3±13.8 (*p=0.110)	21.7±9 (*p=0.056)

BUT: break up time; OSDI: ocular surface disease index.
*Shapiro-Wilk's test (Test of Normality).

TABLE 3: Repeated measures of ANOVA test analysis results. Changes in tear film BUT, Schirmer tests, OSDI scores, mean CCT, TCET and CET values by months.

Months	BUT (p-value)	Schirmer (p-value)	OSDI (p-value)	Mean CCT (p-value)	Mean TCET (p-value)	Mean CET (p-value)
0-1 months	**0.022**	0.167	**<0.001**	**0.004**	0.644	**0.041**
1-3 months	**0.023**	0.460	**<0.001**	0.086	0.058	**0.010**
3-6 months	0.203	0.091	**<0.001**	0.113	0.083	0.111
0-6 months	**<0.001**	0.079	**<0.001**	<0.001	0.423	**0.006**

BUT: break up time; OSDI: ocular surface disease index; CCT: central corneal thickness; TCET: tear and corneal epithelial thickness; CET: corneal epithelial thickness.

DISCUSSION

In the present study, the effects of oral isotretinoin treatment on ocular surface were investigated. The mean CCT, TCET, CET values measured by AS-OCT were evaluated, in addition the mean tear film BUT, Schirmer test, OSDI scores were investigated. Egger had reported the decline in tear film BUT in most cases treated with oral isotretinoin. A pathological decrease of tear film BUT was realized in 69.1 % of the patients.[15] Karalezli et al. found that the mean tear film BUT and Schirmer test results decreased during oral isotretinoin treatment and OSDI scores, impression cytology scores increased with treatment.[16] Polat et al. also found a decrease in Schirmer test with treatment.[17] In our study, the decline during the initial six months in tear film BUT and an increase in OSDI scores were observed. But the Schirmer test was not changed during treatment. In fact, we have already known that isotretinoin affects mainly sebaceous gland activity so the decline in tear film BUT and the stability of the Schirmer test might be expectable.[2,3] The controversy with other reports might be explained by different sample sizes, dosage of the drug and different timing of Schirmer tests.

As mentioned above, studies investigated the effect of oral isotretinoin on impression cytology to find out changes in ocular surface. Karalezli et al. and de Queiroga et al. found alterations in conjunctival epithelium.[16,18]

A few study focused on the mean CCT and anterior segment changes with the treatment. Yuksel et al. obtained statistically significant difference in the mean CCT between baseline and at the sixth month of treatment.[11] The mean CCT decreased gradually during the initial 6 months and correlated with meibomian gland disease score. Cumurcu et al. evaluated the changes in anterior segment parameters as mean CCT, anterior chamber depth (ACD), anterior chamber angle (ACA), lens thickness (LT), pupil size and found statistically significant changes in mean CCT, ACD, LT and keratometric rates.[13] Tear film osmolarity is also an important issue for DED and tear hyperosmolarity is in the definition of DED according to DEWS II report.[19] Deinema et al. found a decrease in CCT with an increase in tear hyperosmolarity.[9] In our study, the mean CCT was measured by AS-OCT and was found to decrease, especially in the first month of the treatment and continued to decline during six months of the treatment.

Both impression cytology and Schiempflug based corneal tomography provide detailed information about ocular surface. Therewithal, AS-OCT provides high resolution imaging. Kal et al. evaluated tear meniscus measured by AS-OCT in advanced renal failure subjects and thought that AS-OCT was useful for evaluating tear meniscus.[20] El-Fayoumi et al. evaluated cornea and corneal epithelial thickness in addition to tear meniscus height in patients with rheumatoid arthritis and found thinner epithelial and corneal thicknesses in these patients.[21] Çakır et al. found an improvement in central corneal epithelial thickness measured by AS-OCT in dry eye patients treated with artificial tear drops.[22] In our knowledge, this study is the first in literature investigating the influence of oral isotretinoin therapy on corneal epithelial thickness measured by AS-OCT. The mean central CET was seen to be affected in the initial three months of treatment. Overall, the difference in mean CET between the baseline and sixth month of treatment was found statistically significant. This change in mean CET was developed with the decrease in tear film BUT and increase in OSDI scores. Totally, we

thought that the changes in the mean CET might be used for assessing the ocular surface.

The main limitation of this study was the absence of data after the cessation of the oral isotretinoin treatment. Besides, relatively small sample size and the manual measurements of corneal epithelial thicknesses were other disadvantages which might have altered the results.

In conclusion, we have already known that the oral isotretinoin treatment might cause dry eye during the therapy. This current study revealed that this treatment might affect the mean CET and CCT measured by AS-OCT. Future studies performed with larger sample sizes and by using more sophisticated AS-OCT types would be more informative about this topic.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Nilgün Özkan Aksoy, Bahar Sevimli Dikicier;* ***Design:*** *Nilgün Özkan Aksoy, Bahar Sevimli Dikicier;* ***Control/Supervision:*** *Erkan Çelik;* ***Data Collection and/or Processing:*** *Nilgün Özkan Aksoy, Burçin Çakır, Bahar Sevimli Dikicier;* ***Analysis and/or Interpretation:*** *Nilgün Özkan Aksoy, , Burçin Çakır;* ***Literature Review:*** *Nilgün Özkan Aksoy, Burçin Çakır, Bahar Sevimli Dikicier;* ***Writing the Article:*** *Nilgün Özkan Aksoy, Burçin Çakır, Bahar Sevimli Dikicier;* ***Critical Review:*** *Bahar Sevimli Dikicier, Erkan Çelik.*

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