Cutaneous and Ocular Toxicology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/icot20

Analysis of corneal topographic and densitometric properties in patients receiving systemic isotretinoin therapy

Mustafa Tosun, Erman Bozali, Duygu Yalınbaş Yeter & Anıl Selim Apa

To cite this article: Mustafa Tosun, Erman Bozali, Duygu Yalınbaş Yeter & Anıl Selim Apa (2023) Analysis of corneal topographic and densitometric properties in patients receiving systemic isotretinoin therapy, Cutaneous and Ocular Toxicology, 42:1, 19-24, DOI: 10.1080/15569527.2022.2152042

To link to this article: https://doi.org/10.1080/15569527.2022.2152042

CUTANEOUS AND OCULAR TOXICOLOGY
2023, VOL. 42, NO. 1, 19–24
https://doi.org/10.1080/15569527.2022.2152042

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

Analysis of corneal topographic and densitometric properties in patients receiving systemic isotretinoin therapy

Mustafa Tosun[a], Erman Bozali[b], Duygu Yalınbaş Yeter[b] and Anıl Selim Apa[b]

[a]Department of Dermatology, Sivas Cumhuriyet University Faculty of Medicine, Sivas, Turkey; [b]Department of Ophthalmology, Sivas Cumhuriyet University Faculty of Medicine, Sivas, Turkey

ABSTRACT

Purpose: To evaluate dry eye parameters, corneal topographic features, corneal densitometric changes, and anterior segment parameters in patients receiving systemic isotretinoin treatment.

Methods: This prospective cross-sectional study included 66 eyes of 33 patients who were started on oral isotretinoin therapy for severe acne vulgaris. All patients were evaluated in terms of ocular surface tests such as tear break-up time (TBUT) and Schirmer-1 and were asked to fill in the ocular surface disease index (OSDI) questionnaire. Corneal densitometric and topographic measurements were obtained using the Scheimpflug imaging system.

Results: The mean age of the patients was 19.9 ± 1.6 years, and 21 (63.6%) of the participants were female. The mean OSDI score was significantly higher in the third month than before treatment (20.05 ± 19.38, vs. 26.96 ± 22.94, $p = 0.00$, respectively). The mean values of the TBUT test were significantly lower in the third month than before treatment (9.06 ± 4.40 sec, vs. 10.71 ± 4.61 sec, $p = 0.02$, respectively). Mean scores of the Schirmer 1 test showed no statistically significant difference between before treatment and the third month (16.08 ± 8.40 mm, vs. 16.08 ± 8.50 mm, $p = 1$, respectively). There was no statistically significant difference between before treatment and the third month in the majority of the densitometry measurements in concentric zones. However, the difference tended to be significant between the groups concerning posterior zone 0–2 mm (11.01 ± 0.85 GSU vs. 10.62 ± 0.89 GSU, $p = 0.006$). The RMS LOAs (front), RMS Total (Total), RMS LOAs Total (Total), RMS HOAs Total (Total), K_{max}, CCT, and CoV values were significantly higher in the third month than before treatment ($p < 0.05$ for all).

Conclusions: The dermatology specialists should be aware of the ocular complications of systemic isotretinoin therapy. Therefore, a complete ophthalmologic examination for the prompt apprehension and management of ocular involvement is essential in patients under isotretinoin therapy to increase ocular comfort and adherence to the therapy.

ARTICLE HISTORY
Received 2 September 2022
Revised 20 October 2022
Accepted 21 November 2022

KEYWORDS
Oral isotretinoin treatment; corneal densitometry; endothelial morphometry

Introduction

Acne is a common inflammatory disease of the skin affecting approximately 9.4% of the world's population [1]. Oral isotretinoin was approved by the United States Food and Drug Administration treatment modality in patients with moderate, severe, and refractory acne [2].

The most common adverse reactions associated with the use of isotretinoin are facial erythema, xerosis, cheilitis, dermatitis, mucositis, vestibulitis, conjunctivitis, epistaxis, and blepharitis [3].

Ocular side effects of isotretinoin consist of atrophy of Meibomian glands, impaired secretion of Meibomian glands, dry eye, blepharoconjunctivitis, keratitis, myopia, optic neuritis, decreased color vision, optic disc edema, and diplopia [4,5].

The definition of dry eye is refined in the TFOS DEWS II Definition and Classification report in 2017 and is described as a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles [6].

The effect of oral isotretinoin on the tear film and ocular surface is well defined and isotretinoin therapy may cause dry eye [7,8]. The side effects of isotretinoin range from changes in the eyelids and cornea to disturbances of the lacrimal fluid leading to dry eye. Dry eye is associated with atrophy of the lacrimal glands and changes in tear film quality and is the most common side effect of isotretinoin use. These changes may have a significant impact on vision-related quality of life, visual function, or future refractive surgery [9,10].

Corneal transparency is essential for optimal vision and all corneal layers must function properly to maintain transparency. The perfect organization of the extracellular matrix of keratocytes, collagen fibres, and stroma, as well as the proper pumping and barrier function of the endothelial layer, are

CONTACT Mustafa Tosun mustafatosun@cumhuriyet.edu.tr Dermatology Department, Sivas Cumhuriyet University School of Medicine, Sivas, 58140, Turkey

essential for maintaining corneal transparency. Various diseases such as corneal degeneration, corneal dystrophy, trauma, infection, and inflammation can cause not only endothelial dysfunction but also loss of transparency or decreased corneal clarity [11–13].

Advances in Scheimpflug imaging systems have enabled quantitative measurement of corneal clarity. Densitometric measurements of the cornea allow evaluation of the cornea's backward light scatter and thus corneal transparency. High corneal densitometry values associated with increased backward light scatter can be observed even in clinically clear corneas without corneal opacity or scarring [11,14]. Corneal densitometry characteristics have been studied in systemic diseases such as rheumatoid arthritis, gout, and diabetes mellitus and ocular diseases such as infectious keratitis, corneal dystrophy, and keratoconus [15–17].

Despite the widespread use of this treatment in the general population, there are only a limited number of studies addressing the ocular adverse effects of systemic isotretinoin.

In the present study, we examined corneal density measurements obtained with the Pentacam-HR Scheimpflug imaging system in patients receiving systemic isotretinoin treatment. We also aimed to investigate dry eye parameters, corneal topographic features, and anterior segment parameters in these patients. To the best of our knowledge, this is the first study to evaluate the changes in corneal densitometry in patients receiving systemic isotretinoin treatment.

Materials and methods

This prospective cross-sectional study was conducted between March and November 2021 at the departments of Dermatology and Ophthalmology of Sivas Cumhuriyet University Hospital. Approval for our study was obtained from the local ethics committee (2021–02/07). Informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

The study included 66 eyes of 33 patients who were referred to the dermatology outpatient clinic and were prescribed isotretinoin treatment at a dose of 0.5 mg/kg/day (a total cumulative dose of 120 mg/kg) for severe acne vulgaris. Participants with a history of trauma, ocular surgery, contact lens use, corneal scarring or opacification, and use of topical ocular medications were excluded. We also excluded patients with ocular diseases such as retinopathy or autoimmune or systemic diseases. All ocular measurements were performed twice, once at baseline and then at the third month of therapy.

Ophthalmologic evaluation

All patients were evaluated with a complete ophthalmologic examination, including the assessment of best-corrected visual acuity (BCVA) using a Snellen chart, measurement of intraocular pressure with a pneumotonometer, and a detailed fundus examination.

Examinations were performed including the ocular surface disease index (OSDI) questionnaire, ocular surface tests such as tear break-up time (TBUT), and the Schirmer-1 test for the diagnosis of dry eye syndrome by the same experienced clinician and all assessments were carried out in the aforementioned order.

The OSDI questionnaire assesses the subjective ocular symptoms of dry-eye disease [18]. Symptoms of dryness were assessed using the standard OSDI questionnaire which consists of twelve questions aimed at inquiring about the patient's dry eye complaints in the last two weeks. This questionnaire consists of three subscales on vision-related symptoms (questions 1–5), ocular symptoms (6–9), and environmental triggers (10–12). The 12 questions of the OSDI questionnaire were graded on a scale of 0–4, with 0 representing 'not once'; 1 representing 'sometimes'; 2 representing 'half of the time'; 3 representing 'most of the time'; and 4 representing 'all of the time.' The OSDI score was calculated by dividing the sum of the patient's responses by the total possible score. In addition to the patient's symptoms, the OSDI allows the assessment of the severity of the condition by evaluating the impact of this discomfort on daily activities, the triggering factors in the environment, and the duration and severity of the discomfort. Higher OSDI scores represent more severe symptoms [19].

The TBUT was measured using a fluorescein strip paper (Fluorescein Sodium Strips, ERC Sağlık, Ankara, Türkiye) moistened with saline solution and then applied to the inferior bulbar conjunctiva. The time interval between the last complete blink and the first visualization of a dry spot or break in the tear film was measured in seconds utilizing the cobalt blue filter of the slit lamp biomicroscope following blinking 3–5 times to form a film over the cornea. The average of three consecutive measurements was recorded [20]. The Schirmer 1 test was performed without anesthesia by inserting a precalibrated filter paper strip (Schirmer Tear Test Strips, ERC Sağlık, Ankara, Türkiye) into the inferotemporal fornix and asking the patient not to squeeze, but only to keep the eyes gently closed. After 5 min, the number of wetted millimeters was recorded [20].

Densitometric and topographic measurements of the cornea were performed with a Scheimpflug imaging system (Pentacam HR; Oculus GmbH, Wetzlar, Germany). Each eye was scanned at least three times, as indicated in the instructions for use of the device, and the most reliable scan that showed the best alignment and fixation was selected for analysis. Corneal topography and anterior segment parameters, including thinnest corneal thickness (CT), anterior chamber depth (ACD), anterior chamber volume (ACV), angle (ACA), maximum keratometry value (Kmax), flat (K1) and steep (K2) keratometry values, and corneal volume (CoV) were measured. In addition, corneal aberrometric values consisting of the root mean square (RMS) of lower-order aberrations (RMS-LOA), RMS of total aberrations (RMS -total), RMS of higher-order aberrations (RMS-HOA), and spherical aberrations from the 6-mm central optical zone were calculated using Pentacam software.

Corneal densitometry was measured automatically utilizing the Pentacam HR densitometry analysis software over a 12-mm diameter of the cornea divided into four concentric zones. The first zone consists of a circular area with a

diameter of two mm in the center of the cornea. The second, third and fourth zones are annular areas surrounding the center with diameters of 2-6 mm, 6-10 mm, and 10-12 mm, respectively. This analysis also provides densitometric values of the cornea at three different depths: the anterior (superficial 120 μm), posterior (60 μm of the innermost cornea), and central (subtracting the anterior and posterior layer thickness from the total thickness) corneal layers. Corneal density measurement values are expressed as pixel luminance per unit volume in the Scheimpflug image and greyscale units (GSU) [13].

All Scheimpflug analysis measurements were performed at the same time of day (between 9 am and 12 pm) to minimize diurnal variation. No pupil dilation was performed during the corneal measurements, and all images were acquired in the same room under the same environmental conditions and dim room lighting. None of the contact lens measurements were taken before the Pentacam HR.

Statistical analysis

Data obtained in the study were analyzed using Statistics Package for Social Sciences (SPSS) version 22.0 software. Continuous variables were expressed as mean ± standard deviation (SD), median, and range values; categorical variables were expressed as number (*n*) and percentage (%). Whether the distribution of continuous data was normal or not was examined using the Kolmogorov–Smirnov test. The paired *t*-test was used to determine the difference between continuous variables with normal distribution in repeated measures. The Wilcoxon test was used for repeated variables that did not have a normal distribution. A value of $p < 0.05$ was accepted as statistically significant.

Results

The mean age of the total study population was 19.9 ± 1.6 years, and 21 (63.6%) of the participants were female. Mean values of OSDI score were significantly higher in the third month than before treatment (20.05 ± 19.38, vs. 26.96 ± 22.94, $p = 0.00$). Mean scores of the TBUT test were significantly lower in the third month than before treatment (9.06 ± 4.40 s, vs. 10.71 ± 4.61 s, $p = 0.02$). Mean scores of the Schirmer 1 test showed no statistically significant difference between before treatment and the third month (16.08 ± 8.40 mm, vs. 16.08 ± 8.50 mm, $p = 1$) (Table 1).

We found that most of the densitometry measurements in concentric zones were not statistically significant differences between before treatment and the third month when we compared the corneal densitometry values of the groups. However, the difference tended to be significant between the groups concerning posterior zone 0–2 mm (11.01 ± 0.85 GSU vs. 10.62 ± 0.89 GSU, $p = 0.006$) (Table 2). We found that RMS LOAs (front) (1.47 ± 0.39 vs. 1.55 ± 0.5, $p = 0.039$), RMS Total (Total) (1.27 ± 0.38 vs. 1.4 ± 0.56, $p = 0.012$), RMS LOAs Total (Total) (1.22 ± 0.38 vs. 1.33 ± 0.51, $p = 0.019$), RMS HOAs Total (Total) (0.33 ± 0.08 vs. 0.37 ± 0.16, $p = 0.036$), Kmax (diopters) (43.45 ± 1.11 vs.43.69 ± 1.34, $p = 0.002$), CT (μm) (540.35 ± 28.68 vs.542.81 ± 28.07 $p = 0.007$), and CoV (mm^3) (60.38 ± 2.96 vs. 60.65 ± 2.91, $p = 0.007$) values were significantly higher in the third month than before treatment. Other values were similar between groups (Table 3).

Table 1. Demographics and clinical features of the patients.

Age (years), mean ± SD		19.9 ± 1.6
Gender, *n* (%)		
Female		21 (63.6)
Male		12 (36.4)
OSDI, mean ± SD		*p* Value*
Month 0	20.05 ± 19.38	**0.00**
3rd Month	26.96 ± 22.94	
TBUT test, sec, mean ± SD		*p* Value*
Month 0	10.71 ± 4.61	**0.02**
3rd Month	9.06 ± 4.40	
Schirmer 1 test, mm, mean ± SD		*p* Value*
Month 0	16.08 ± 8.40	1.00
3rd Month	16.08 ± 8.50	

*Paired *T*-test; $p < 0.05$.
TBUT: tear break-up time; OSDI: Ocular Surface Disease Index.

Table 2. Corneal densitometry measurements of the patients.

	Month 0 *n*:33	3rd Month *n*:33	*p* Value*
Anterior (120 μm) (GSU)			
0–2 mm	24.06 ± 1.63	23.88 ± 1.77	0.3
2–6 mm	21.46 ± 1.32	21.3 ± 1.44	0.3
6–10 mm	19.5 ± 2.27	19.32 ± 2.22	0.5
10–12 mm	30.46 ± 6.04	31.71 ± 7.79	0.2
Total (0–12 mm)	22.7 ± 1.59	22.44 ± 3.56	0.6
Centre (GSU)			
0–2 mm	14.97 ± 0.81	14.91 ± 0.88	0.6
2–6 mm	13.21 ± 0.66	13.18 ± 0.68	0.7
6–10 mm	12.18 ± 1.15	12.28 ± 0.93	0.4
10–12 mm	18.32 ± 2.48	18.83 ± 2.89	0.1
Total (0–12 mm)	14.0 ± 0.77	14.1 ± 0.8	0.4
Posterior (60 μm) (GSU)			
0–2 mm	10.62 ± 0.89	11.01 ± 0.85	0.006
2–6 mm	10.06 ± 0.69	11.41 ± 11.66	0.4
6–10 mm	10.52 ± 0.87	10.18 ± 1.57	0.1
10–12 mm	13.77 ± 2.44	14.15 ± 1.64	0.2
Total (0–12 mm)	11.04 ± 0.72	10.84 ± 0.73	0.058
Total thickness (GSU)			
0–2 mm	16.67 ± 0.94	16.48 ± 1.02	0.1
2–6 mm	14.91 ± 0.77	14.72 ± 0.81	0.09
6–10 mm	14.07 ± 1.37	14.06 ± 1.09	0.9
10–12 mm	20.94 ± 2.98	21.51 ± 3.73	0.2
Total (0–12 mm)	15.93 ± 0.86	15.94 ± 1.0	0.9

*Paired *t*-test.
GSU: greyscale units.

Discussion

In this current study, we evaluated dry eye parameters, corneal topographic features, corneal densitometric changes, and anterior segment parameters in patients receiving systemic isotretinoin treatment. Our results demonstrated that mean values of OSDI scores were significantly higher and mean scores of the TBUT test were significantly lower in the third month than before treatment. Mean scores of the Schirmer 1 test and most of the densitometry measurements in concentric zones were not statistically significant differences between before treatment and the third month. However, the difference tended to be significant between the groups concerning posterior zone 0–2 mm. We found that RMS LOAs (front), RMS Total (Total), RMS LOAs Total (Total), RMS HOAs Total (Total), Kmax (diopters), CT (μm), and

Table 3. Comparison of aberrometric values, anterior segment, and corneal topographical parameters of the study population.

	Month 0 *n*:33	3rd Month *n*:33	*p* Value*
RMS total (front)	1.53 ± 0.42	1.6 ± 0.51	0.1
RMS LOAs (front)	1.47 ± 0.39	1.55 ± 0.5	**0.039**
RMS HOAs (front)	0.34 ± 0.08	0.37 ± 0.14	0.066
SA (front)	0.22 ± 0.05	0.21 ± 0.07	0.3
RMS total (back)	0.76 ± 0.13	0.76 ± 0.12	0.8
RMS LOAs (back)	0.74 ± 0.13	0.74 ± 0.12	0.8
RMS HOAs (back)	0.17 ± 0.02	0.17 ± 0.02	0.1
SA (back)	−0.14 ± 0.02	−0.14 ± 0.02	0.3
RMS total (total)	1.27 ± 0.38	1.4 ± 0.56	**0.012**
RMS LOAs total (total)	1.22 ± 0.38	1.33 ± 0.51	**0.019**
RMS HOAs total (total)	0.33 ± 0.08	0.37 ± 0.16	**0.036**
SA (total)	0.17 ± 0.05	0.16 ± 0.07	0.2
K1 (diopters)	42.05 ± 1.15	42.08 ± 1.17	0.1
K2 (diopters)	41.84 ± 6.29	43.14 ± 1.24	0.1
Kmax (diopters)	43.45 ± 1.11	43.69 ± 1.34	**0.002**
CT (μm)	540.35 ± 28.68	542.81 ± 28.07	**0.007**
CoV (mm^3)	60.38 ± 2.96	60.65 ± 2.91	**0.007**
ACV (mm^3)	199.5 ± 25.06	200.43 ± 24.2	0.5
ACD (mm)	3.15 ± 0.23	3.16 ± 0.25	0.059
ACA (degrees)	40.79 ± 4.62	41.13 ± 3.55	0.5

*Paired *t*-test; $p < 0.05$.

RMS: root mean square; LOAs: low order aberrations; HOAs: high order aberrations; SA: spherical aberrations; K1: flat keratometry; K2: steep keratometry; Kmax: maximum keratometry; CT: thinnest corneal thickness; CoV: corneal volume; ACV: anterior chamber volume; ACD: anterior chamber depth; ACA: anterior chamber angle.

CoV (mm^3) values were significantly higher in the third month than before treatment. Other values were similar between groups.

Isotretinoin is one of the most effective treatments for moderate and severe acne. One of the main side effects is ocular surface disease. The ocular surface is the most affected structure when isotretinoin is used. However, several studies also reported changes in measurements in the posterior segment of the eye [21].

Adverse effects affecting the ocular surface, dry eye symptoms, including blepharoconjunctivitis, subepithelial corneal opacities, and contact lens intolerance, are among the most common complications of isotretinoin therapy. In the literature, *in vitro* studies have shown that isotretinoin causes cell apoptosis and dysfunction in Meibomian glands by inhibiting cell proliferation in Meibomian glands and releasing inflammatory mediators [4]. Similarly, isotretinoin may affect Meibomian gland function, which would explain problems such as blepharitis and meibomitis during therapy since there are similarities between the sebaceous glands and the Meibomian glands in the skin [7].

The OSDI score, presence of dry eye disease (DED), and evaluation of the tear film functions such as the Schirmer test and TBUT measurements have been commonly investigated in patients receiving systemic isotretinoin therapy. In previous studies, a significant increase in OSDI score was observed in patients treated with isotretinoin [5,7,22–24]. Similarly, in our study, the mean values of OSDI scores were found to be significantly increased with isotretinoin treatment. The use of isotretinoin was significantly associated with a lower mean TBUT [8,25,26]. Similarly, the mean values of the TBUT test were significantly lower under isotretinoin therapy in our study. The Schirmer-1 test is performed without anesthesia and assesses the volume of tears produced by the ocular surface using filter paper strips. Some studies reported that isotretinoin use was significantly associated with a reduction in the scores of the Schirmer 1 test [5,22,23,25–28]. However, other studies reported no statistically significant difference in Schirmer scores before and during isotretinoin therapy [28,29]. Our results demonstrated no significant difference between before treatment and the third month of therapy regarding the mean values of the Schirmer 1 test. An anesthetized Schirmer test assessing basal tear secretion shows higher sensitivity than the standard Schirmer test in detecting decreased tear production in patients with Sjögren syndrome, a disease characterized by the involvement of the lacrimal gland. In their study, Karalezli et al. found the anesthetized Schirmer test to be significantly lower in patients using isotretinoin, while they did not observe that the Schirmer test without anesthesia was significant [7]. Çağlar et al. found the Schirmer test not significant during isotretinoin treatment, and Schirmer test 1 has no useful effect on the diagnosis of evaporative dry eye associated with Meibomian gland disease-causing isotretinoin treatment. They reported that the test does not need to be performed during treatment [22].

Oral isotretinoin causes significant changes in the cornea, especially the anterior layer. The cornea is the most sensitive and densely innervated tissue in the body. A previous study found that corneal sensitivity decreased significantly in patients treated with isotretinoin after 3 months [10].

Corneal densitometry provides quantitative measurements of corneal transparency and clarity. The main sources of light scatter in the cornea are the corneal endothelium and the corneal epithelial Layer [16]. The results of the present study showed that there was an increase in corneal densitometry value of the posterior zone 0–2 mm in patients on the third month of receiving systemic isotretinoin treatment. Other corneal densitometry values did not show a significant difference between patients before treatment and the third-month receiving systemic isotretinoin therapy. In the study that evaluated the change of corneal epithelial thickness in patients receiving isotretinoin treatment, Ozyol et al. found isotretinoin treatment induces epithelial thickening and stromal thinning [30]. The changes in epithelial thickness have been controversial in dry eye disease. Cui et al. have reported thinner corneal epithelium in the dry eye group whereas Kanellopoulos et al. have reported increased epithelial thickness [31,32].

The optical surface becomes irregular and unstable thus may cause further aberrations or unpredictable keratometry measurements when the tear film is disrupted [33]. Therefore, the outcome of dry eye on corneal topography parameters is controversial in the literature. Dogan et al. reported no significant difference between dry eye patients and healthy controls in terms of keratometry where Nagy et al. reported increased keratometric data in patients with systemic sclerosis [33,34]. In our study, we also observed increased Kmax values in accordance with the latter study. This conflicting results may be due to the change in the behaviour of the cornea.

The higher optical aberrations in patients with dry eyes have been found to be related to tear-film irregularity and its decreasing stability [35]. Koh et al. also reported increased

HOAs in patients with dry eye who had superficial punctate keratopathy [36]. Similarly, in our study, RMS LOAs (front), RMS Total (Total), RMS LOAs Total (Total), and RMS HOAs Total (Total) were significantly increased by isotretinoin therapy.

The CCT is an indicator of corneal health demonstrating the changes in corneal metabolism and hydration status [37]. Fujimato et al. observed that central corneal thickness was increased in mild and severe DED [38]. However, Zhao et al. found no significant difference between dry eye and non-dry eye groups in terms of CCT in people undergoing corneal refractive surgery to correct myopia [39]. The reason for the increased CCT difference in dry eye may be due to Pentacam being less susceptible to tears [40]. In conjunction with the first aforementioned study, we also found that the CCT was increased after isotretinoin therapy which leads to dry eye.

In a recent study by Nagy et al., they observed no significant difference regarding CV between patients with systemic sclerosis suffering from dry eye and healthy controls. On the contrary, the CV was increased in our study population. This increase may be explained by the increased corneal thickness [34].

There are some limitations to our study. First, the properties of corneal endothelial cells could not be examined by specular microscopy. Second, this study was performed with small sample size and in a single center. Further comprehensive studies of ocular involvement in patients receiving systemic isotretinoin treatment are needed in the future.

In conclusion, dermatology specialists should be aware of the ocular complications of systemic isotretinoin therapy. Even though we observed that isotretinoin therapy does not lead to significant corneal densitometric alterations, we demonstrated significant differences regarding corneal aberrations and properties. Therefore, a complete ophthalmologic examination including dry eye tests such as Schirmer 1 and TBUT for the prompt apprehension and management of ocular involvement is essential in patients under isotretinoin therapy thus not only increasing the ocular comfort of the patients but also the adherence to the therapy.

Acknowledgements

There is no funding in this study.

Ethical approval

Approval for our study was obtained from the local ethics committee (2021–02/07).

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

ORCID

Mustafa Tosun http://orcid.org/0000-0002-6189-8016
Erman Bozali http://orcid.org/0000-0001-7918-8381
Duygu Yalınbaş Yeter http://orcid.org/0000-0001-9001-0277

References

1. Tan JK, Bhate K. A global perspective on the epidemiology of acne. Br J Dermatol. 2015;172:3–12.
2. Yavuz C, Ozcimen M. An evaluation of peripapillar choroidal thickness in patients receiving systemic isotretinoin treatment. Cutan Ocul Toxicol. 2019;38(1):25–28.
3. Layton A. The use of isotretinoin in acne. Dermatoendocrinol. 2009;1(3):162–169.
4. Ruiz-Lozano RE, Hernández-Camarena JC. Isotretinoin and the eye: a review for the dermatologist. Dermatologic Therapy. 2020;33:e14029.
5. Düzgün E, Özkur E. The effect of oral isotretinoin therapy on meibomian gland morphology and dry eye tests. J Dermatolog Treat. 2022;33(2):762–768.
6. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. Ocul Surf. 2017;15(3):276–283.
7. Karalezli A, Borazan M, Altinors DD, et al. Conjunctival impression cytology, ocular surface, and tear-film changes in patients treated with systemic isotretinoin. Cornea. 2009;28(1):46–50.
8. Cumurcu T, Sezer E, Kilic R, et al. Comparison of dose-related ocular side effects during systemic isotretinoin administration. Eur J Ophthalmol. 2009;19(2):196–200.
9. Santodomingo-Rubido J, Barrado-Navascués E, Rubido-Crespo MJ. Drug-induced ocular side-effects with isotretinoin. Ophthalmic Physiol Opt. 2008;28(5):497–501.
10. Fouladgar N, Khabazkhoob M, Hanifnia AR, et al. Evaluation of the effects of isotretinoin for treatment of acne on corneal sensitivity. J Curr Ophthalmol. 2018;30(4):326–329.
11. Karmiris E, Soulantzou K, Machairoudia G, et al. Corneal densitometry assessed with scheimpflug camera in healthy corneas and correlation with specular microscopy values and age. Cornea. 2022;41(1):60–68.
12. Tekin K, Sekeroglu MA, Kiziltoprak H, et al. Corneal densitometry in healthy corneas and its correlation with endothelial morphometry. Cornea. 2017;36(11):1336–1342.
13. Cankaya C, Cumurcu T, Gunduz A. Corneal endothelial changes in patients with vitamin D deficiency. Indian J Ophthalmol. 2018;66(9):1256–1261.
14. Wegener A, Laser-Junga H. Photography of the anterior eye segment according to Scheimpflug's principle: options and limitations – a review. Clin Exp Ophthalmol. 2009;37(1):144–154.
15. Ní Dhubhghaill S, Rozema JJ, Jongenelen S, et al. Normative values for corneal densitometry analysis by Scheimpflug optical assessment. Invest Ophthalmol Vis Sci. 2014;55(1):162–168.
16. Anayol MA, Bostancı B, Şekeroğlu MA, et al. Assessment of corneal densitometry in rheumatoid arthritis patients. Turk J Ophthalmol. 2017;47(3):125–129.
17. Kosekahya P, Atilgan KG, Atilgan CU, et al. Could corneal densitometry be used as a diagnostic and screening tool for ocular involvement in patients with gout? Int Ophthalmol. 2019;39(5):991–1001.
18. Wolffsohn JS, Arita R, Chalmers R, et al. TFOS DEWS II diagnostic methodology report. Ocul Surf. 2017;15(3):539–574.
19. Schiffman RM, Christianson MD, Jacobsen G, et al. Reliability and validity of the ocular surface disease ındex. Arch Ophthalmol. 2000;118(5):615–621.
20. Bron AJ, Abelson MB, Ousler G, et al. Methodologies to diagnose and monitor dry eye disease: report of the diagnostic methodology subcommittee of the ınternational dry eye WorkShop (2007). Ocular Surface. 2007;5:108–152.
21. Sekeryapan Gediz B, Corak Eroglu F, Aydogan M, et al. Choroidal vascular changes in acne patients under isotretinoin treatment. Cutan Ocul Toxicol. 2021;40(2):125–129.

22. Caglar C, Senel E, Sabancilar E, et al. Reduced ocular surface disease index (OSDI) scores in patients with isotretinoin treatment. Int Ophthalmol. 2017;37(1):197–202.
23. Elhamaky TR. Efficacy of omega-3 fatty acids and punctal plugs in the prevention of isotretinoin-associated ocular surface disease. Eur J Ophthalmol. 2021;31(5):2339–2345.
24. Tanriverdi C, Nurozler Tabakci B, Donmez S. Longitudinal assessment of meibomian glands and tear film layer in systemic isotretinoin treatment. Eur J Ophthalmol. 2022;32(2):885–893.
25. 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.
26. Oner A, Ferahbas A, Karakucuk S, et al. Ocular side effects associated with systemic isotretinoin. J Toxicol. 2005;23:189–195.
27. Polat M, Kükner Ş. The effect of oral isotretinoin on visual contrast sensitivity and amount of lacrimation in patients with acne vulgaris. Cutan Ocul Toxicol. 2017;36(1):35–38.
28. Bozkurt B, Irkeç MT, Atakan N, et al. Lacrimal function and ocular complications in patients treated with systemic isotretinoin. Eur J Ophthalmol. 2002;12(3):173–176.
29. Mathers WD, Shields WJ, Sachdev MS, et al. Meibomian gland morphology and tear osmolarity: changes with accutane therapy. Cornea. 1991;10(4):286–290.
30. Ozyol P, Ozyol E, Yildirim FE. Remodeling of cornea with isotretinoin treatment. Eye Contact Lens. 2021;47(6):366–371.
31. Kanellopoulos AJ, Asimellis G. In vivo 3-dimensional corneal epithelial thickness mapping as an indicator of dry eye: preliminary clinical assessment. Am J Ophthalmol. 2014;157(1):63–68.e2.
32. Cui X, Hong J, Wang F, et al. Assessment of corneal epithelial thickness in dry eye patients. Optom Vis Sci. 2014;91(12):1446–1454.
33. Doğan AŞ, Gürdal C, Köylü MT. Does dry eye affect repeatability of corneal topography measurements? Turk J Ophthalmol. 2018;48(2):57–60.
34. Nagy A, Rentka A, Nemeth G, et al. Corneal manifestations of systemic sclerosis. Ocul Immunol Inflamm. 2019;27(6):968–977.
35. Yildirim Y, Ozsaygili C, Kucuk B. The short term effect of trehalose and different doses of sodium hyaluronate on anterior corneal aberrations in dry eye patients. Cutan Ocul Toxicol. 2021;40(1):14–20.
36. Koh S, Maeda N, Hirohara Y, et al. Serial measurements of higher-order aberrations after blinking in patients with dry eye. Invest Ophthalmol Vis Sci. 2008;49(1):133–138.
37. Lattimore MR, Jr Kaupp S, Schallhorn S, et al. Orbscan pachymetry: implications of a repeated measures and diurnal variation analysis. Ophthalmology. 1999;106(5):977–981.
38. Fujimoto K, Inomata T, Okumura Y, et al. Comparison of corneal thickness in patients with dry eye disease using the pentacam rotating scheimpflug camera and anterior segment optical coherence tomography. PLOS One. 2020;15(2):e0228567.
39. Zhao PF, Zhou YH, Hu YB, et al. Evaluation of preoperative dry eye in people undergoing corneal refractive surgery to correct myopia. Int J Ophthalmol. 2021;14(7):1047–1051.
40. Chen D, Lam AK. Reliability and repeatability of the pentacam on corneal curvatures. Clin Exp Optom. 2009;92(2):110–118.