Effect of Oral Isotretinoin on The Thickness of Retinal Layers

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ABSTRACT

Purpose: To analyze detailed changes in retinal layers thickness with spectral domain-optical coherence tomography (SD-OCT) in isotretinoin users.

Methods: This study included two groups as 40 patients who were using at least 1-year oral isotretinoin for nodulocystic acne and 40 healthy volunteers. Care was taken to ensure that the two groups were homologous in age and sex (14 male and 26 female). The right eyes of subjects examined in this study. All patients underwent complete ophthalmologic examination. SD-OCT(spectral-domain optical coherence tomography) images were developed from Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany)and it is capable of using a new algorithm that could measure retinal layers around the macula. These measurements include; retinal pigment epithelium layer (RPE), outer plexiform layer (OPL), outer nuclear layer (ONL), inner nuclear layer (INL), inner plexiform layer (IPL), ganglion cell layer (GCL), retinal nerve fiber layer (RNFL), total retinal thickness (Retina).

Results: The mean age was 22.35±1.97 years in isotretinoin users and 21.33±2.20 years in the control group. The average time of isotretinoin medication was 12.78 ± 1.00 months (12-16 months). We found no statistically significant difference with respect to the retinal layer and total retinal thickness at 1mm, 3mm, and 6 mm rings between the isotretinoin user and control groups

Conclusion: Isotretinoin has no undesirable effect on the thickness of retinal segments.

Key Words: Retinal layers; spectral-domain optical coherence tomography; isotretinoin.

INTRODUCTION

Isotretinoin is a vitamin A derivative synthetic retinoid, the most important and most commonly used therapeutic agent for severe cystic and nodular acne.[1-2] The most common side effects of isotretinoin are on mucocutaneous membranes (e.g.dry eye, cheilitis, dry skin) although it can affect all systems (e.g. central-peripheric nervous system, hematologic systems and gastrointestinal).[3] Using this drug could effect almost all ocular tissues and lead to some dose related adverse effects such as abnormal meibomian gland functions, dry eyes, blepharoconjunctivitis, corneal opacities, blurry vision, keratitis, photophobia, reduced dark adaptation, photophobia, retinal abnormalities, optic neuropathy, visual field defects.[4] Although the study of the effect of isotretinoin on individual retinal layers has not been previously available, some studies have shown its effect on RNFL and GCL, in particular.[8-12] It has been hypothesized that RNFL thinning may be an important marker for follow-up in oral isotretinoin users.[10]

In this study, we intended to examine the consequences of using isotretinoin on every retinal layers thickness by measuring spectral domain-optical coherence tomography (SD-OCT).

MATERIALS AND METHODS

Ophthalmology and Dermatology clinics of the University Hospital participated in this prospective, cross-sectional study. 40 eyes of 40 patients using oral isotretinoin therapy at least one year and 40 sex and age-matched (14 male and 26 female) healthy subjects involved in this research. The right eyes of subjects examined in this study. Doses of isotretinoin was 0.5 mg/kg/day. The cumulative isotretinoin dose during the study was 120 to 150mg/kg. Target cumulative dose was 150mg/kg.

All eyes were given an ocular evaluation including autorefraction, visual acuity testing (Snellen), intraocular pressure (Non-contact tonometry) and slit-lamp

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biomicroscopic examination before measurement. % 1 tropicamide eye drops were used for pupil dilation. SD-OCT images were made by a certain researcher and completed according to the instructions manual. All images were obtained from 9.00 to 12.00 am to avoid diurnal fluctuation. New segmentation software allows for analyzing each layer of the retina. These measurements contain: retinal pigment epithelium (RPE) layers outer plexiform layer (OPL), outer nuclear layer (ONL), inner nuclear layer (INL), inner plexiform layer (IPL), ganglion cell layer (GCL), retinal nerve fiber layer (RNFL), total retinal thickness (Retina) (Figure 1). Furthermore, the thickness of outer retinal layers (ORL) and inner retinal layers (IRL) given by the Automated segmentation device of the posterior pole scan. The measurement of all layer on central (1mm)-inner (3 mm) and outer (6 mm) rings as indicated in the Early Treatment Diabetic Retinopathy Study (ETDRS).[5]

Our research adopted the principles set out in the Helsinki Declaration. Written informed consent was obtained from all participants for sample collection and analysis. Sureyyapasa Research and Training Hospital Ethics Committee of Clinical Research approved the study protocol.

The participants who had ocular disease history, axial length (AL) >25 mm, spherical equivalent of less than -1 and greater than +1, previous eye surgery, any ocular or systemic disease and taking any medication within the last 3 months were excluded in this study.

Statistical Analysis

Statistical Package for the Social Sciences software (SPSS v17.0; SPSS Inc., Chicago, IL, USA) used for all statistical analysis. Normal distribution was evaluated using the Kolmogorov-Smirnov test. Descriptive data presented as mean±standard deviations. In order to compare qualitative values with normal distribution Student's t-test and compare parameters without normal distribution the Mann-Whitney U-test were used. Statistical significance was set at $p<0.05$.

RESULTS

Our study included 80 age and sex matched participants. All participants right eyes selected and they were divided into 40 patients who used oral isotretinoin for nodulocystic acne with at least one-year treatment (14 male and 26 female) and 40 healthy subjects (26 female and 14 male). The mean age was 22.35±1.97 years in isotretinoin users and 21.33±2.20 years in the control group. The mean IOP was 16.42±2.88 mmHg in the isotretinoin patients group while in the healthy volunteer group was 17.93±3.51 mmHg. The mean time of medication was 12.78 ± 1.00 months (12-16 months).

There were no significant differences between the isotretinoin users and control groups in the measurements of Retina, RNFL, GCL, IPL, INL, OPL, ONL, RPE, IRL, ORL layer thickness in the central(1mm)-inner(3 mm) and outer(6 mm) rings (Table 1).

DISCUSSION

The main mechanism of isotretinoin is on cell growth and differentiation. Since retinoic acid prevents proliferation in glial and RPE cells it may also affect recovery in patients with PVR and retinal detachment.[6-7]

Many studies have commonly focused on examining the

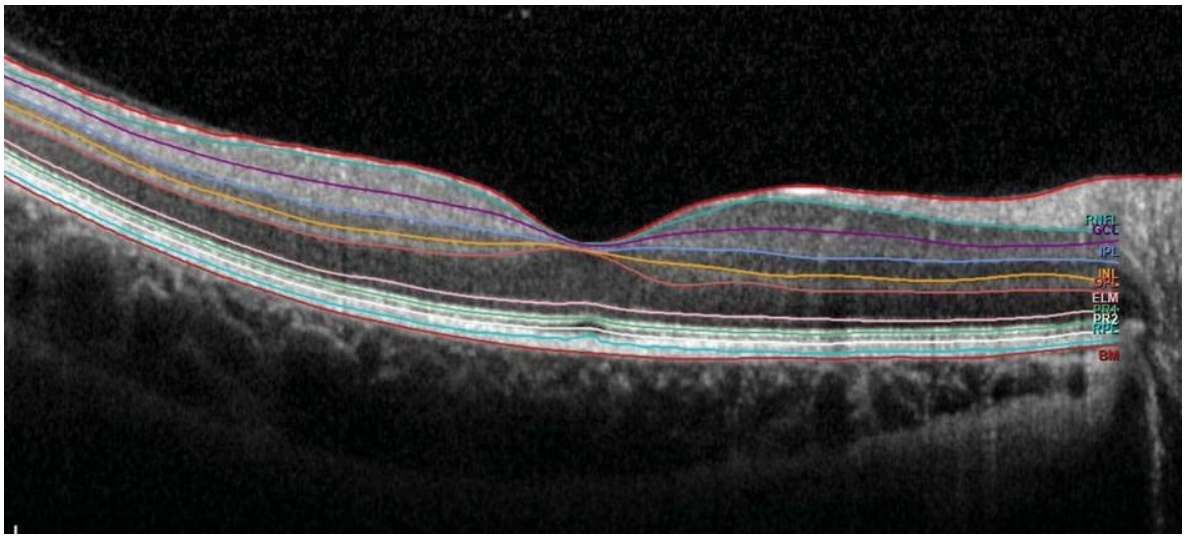

Figure 1. *Retinal layer automatic segmentation with Spectralis optical coherence tomography.*

Retinal nerve fiber layer (RNFL); ganglion cell layer (GCL); inner plexiform layer (IPL); inner nuclear layer (INL); outer plexiform layer (OPL); outer nuclear layer (ONL); inner retinal layers (IRL) and outer retinal layers (ORL) (Figure 1).

Table 1. *Mean layers thickness as measured by Heidelberg SD-OCT for oral isotretinoin treatment patients and controls.*

	Central ring (mean±SD)			*Inner Ring (mean±SD)*			*Outer Ring (mean±SD)*		
	İsotretinoin users (µm)	Control (µm)	p	İsotretinoin users (µm)	Control (µm)	p	İsotretinoin users (µm)	Control (µm)	p
Retina	255,45±14,23	257,41±16,32	.586	331,91±12,59	335,62±13,42	.228	296,68±9,75	299,47±11,45	.265
RNFL	10,94±1,48	11,30±2,17	.412	21,72±1,72	21,16±1,72	.173	37,12±3,66	35,52±4,88	.117
GCL	13,64±3,00	13,66±3,79	.982	52,10±3,85	51,61±3,98	.601	36,97±3,30	36,81±2,92	.836
IPL	19,63±2,35	19,55±2,88	.894	41,59±2,78	41,04±2,82	.410	29,61±2,20	29,68±2,08	.902
INL	16,41±2,66	14,69±3,36	.019	38,02±3,21	38,06±2,34	.950	33,028±1,71	33,18±1,89	.721
OPL	23,63±5,04	22,00±5,38	.187	32,40±3,33	33,66±5,37	.235	26,28±1,75	27,94±3,03	.006
ONL	86,55±8,13	90,66±8,08	.035	66,81±6,43	70,46±7,27	.027	55,70±4,69	59,11±6,59	.014
RPE	16,88±1,61	15,88±1,36	.006	13,74±1,22	13,66±1,15	.786	12,55±1,12	12,57±1,11	.914
IRL	169,11±14,16	170,44±16,64	.715	250,28±15,45	255,97±12,18	.087	218,21±9,47	222,38±11,53	.099
ORL	86,55±3,71	86,97±3,37	.620	79,52±1,84	80,28±2,00	.100	77,48±1,96	77,96±1,94	.302

RNFL; retinal nerve fiber layer; GCL;ganglion cell layer; IPL; inner plexiform layer; INL; inner nuclear layer; OPL; outer plexiform layer; ONL; outer nuclear layer; RPE; retinal pigment epithelium; IRL; inner retinal layers; ORL; outer retinal layers.

impact of oral isotretinoin on GCL and RNFL thickness. Spectral-domain OCT (SD-OCT) was used to establish the presence of RNFL defects in some patients who used isotretinoin.[8-14] Dinc et al. reported a case who had bilateral optic nerve atrophy in which decreased RNFL thickness was related to the receiving isotretinoin therapy for acne vulgaris. [8] Kapti et al. found initial RNFL thickness to be similar to the first and sixth posttreatment months' RNFL measurements in patients receiving oral isotretinoin treatment in their study.[9] Ucak et al. could not find any difference between pre and posttreatment mean GCL thickness and relationship between the duration of treatment and the thickness of RNFL and GCL in a mean of 5.4 months of follow-up. However, they found RNFL thickness temporal inferior quadrant to be thinner compared to the onset and also stated that the regional thinning of RNFL (temporal inferior quadrant) could be an important marker in assessing the potential adverse effects of isotretinoin therapy on the retina. [10] In another study by Sekeryapan et al., no difference was found between the RNFL and GCL thickness in the eyes of 28 isotretinoin user patients in four to eight months follow up [11]. Isotretinoin can cause visual field defects.[4] Therefore, Bakbak et al. examined visual field and peripapillary RNFL measurement patients who were treated with isotretinoin and could not find any significant difference in the three months follow up.[12] Yilmaz et al. measured RNFL and macular OCT baseline every month for three months in their study which included 36 patients who received isotretinoin therapy and each month, the temporal quadrants were significantly thinner than the baseline RNFL measurement. They also found the superior, temporal and nasal outer quadrants in macular measurements to be significantly thinner on the second and third month when compared with the initial and first month measurements. [13] Demirok et al. examined the effect of using oral isotretinoin for one year on ganglion cell layer (GCL) thickness by performing optical coherence tomography (SD-OCT) on the first, third, sixth and 12th months and did not find a significant difference between the measurements.[14] Our study was in line with the studies mentioned in terms of GCL and RNFL measurement results. We did not find any significant differences in the retinal layer analyses. However, the RPE thickness in the central ring (1 mm) was higher in the isotretinoin user group and the OPL thickness in the outer ring (6mm) was thinner in the isotretinoin user group (p:0.06; p:0.06, respectively). Therefore, we can hypothesize that some retinal layers changes could be or may be an early indicator of toxic effects of isotretinoin on the retina.

There are also studies in the literature evaluating the electrophysiological changes in the patients who used isotretinoin. Weleber et al. performed electrophysiological tests including electroretinography (ERG) and electrooculography (EOG) to examine optic nerve functions in their studies which included three patients who used oral isotretinoin. Although there was no changes in EOG, there were abnormalities in the ERG such as elevations in the dark adaptation wave of cone and rod responses especially during drug use.[15] Since night blindness can be permanent, some studies strongly suggest that patients should consider discontinuing the isotretinoin as soon as night blindness develops.[4] In our study, none of the participants in the isotretinoin users group described night blindness.

Similarly, Aydoğan et al. reported increased delay of P100 waves in visual evoked potentials (VEP) after oral isotretinoin treatment in six of 32 patients, however, this result was not significant.[16]

We intended to compare the thickness of the all retinal layers with healthy individuals and patients receiving oral isotretinoin therapy in the present study. Our results indicated that there were no significant differences in the groups' RNFL, ganglion cell complex thicknesses and each retinal segments. To the best of our knowledge, this is the first study to individually asses the retinal layer thickness in patients using isotretinoin. However, our study had some limitations. The greatest deficiency of our study was not to support our findings with electrophysiological tests such as VEP, ERG. Another limitation was the relatively smaller study population and not using any color vision or visual field tests. Finally, another major limitation to our study was the fact that it was cross-sectional and there was an absence of SD-OCT images of the pre-treatment patient group. Therefore, considering the increased use of isotretinoin, we believe that further studies should be conducted to understand the morphological and physiological effects of isotretinoin on the retina more clearly.

CONCLUSIONS

In conclusion, we observed that the oral isotretinoin has no undesirable effect on the thickness of retinal segments.

Declaration of Interest

No conflict of interest is between the authors. The authors alone are responsible for the content and writing of this article**.**

Disclosure Statement

All authors declare that they do not have affiliations or participation with any association or agency with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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