

Comparison of Dose-Related Isotretinoin Effects on SD-OCT Parameters in Patients with Acne Vulgaris

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ABSTRACT

Purpose: To compare the effects of high- (Group 1) and low-dose (Group 2) systemic isotretinoin effects on spectral domain optic coherence tomography parameters in patients with acne vulgaris.

Material and methods: Thirty patients receiving high-dose (>0.5 mg/kg per day) systemic isotretinoin treatment and 32 patients treated with low-dose systemic isotretinoin (<0.5 mg/kg per day) were enrolled. Subfoveal choroidal thickness (SFCT), peripapillary retinal nerve fibre layer (pRNFL) and macular ganglion cell complex (mGCC) thicknesses were evaluated at before the treatment, at fourth month visit and one month after the cessation of treatment.

Results: There was no statistically significant difference in mGCC thickness and SFCT values between the two groups during the study ($p>0.05$). But, at the fourth month visit, temporal and inferior quadrants of pRNFL in patients received high dose isotretinoin were significantly lower than patients received low dose ($p=0.037$ and $p=0.041$, respectively). At the one month after the cessation of treatment, only temporal quadrant of pRNFL in Group 1 was significantly lower than Group 2 ($p=0.033$). No statistically significant difference was observed in other quadrants of pRNFL and mean pRNFL between two groups during the study.

Conclusion: Low dose isotretinoin seems to have safety profile for SFCT, mGCC and pRNFL. However, according to our results, high dose isotretinoin caused pRNFL thinning while caused no SFCT and mGCC thinning. High dose therapy may have a toxic effect on pRNFL, especially temporal and inferior quadrant. Therefore, it may be useful to monitor patients receiving high doses in clinical practice with the SD-OCT.

Keywords: Acne vulgaris, Ganglion cell complex, Isotretinoin therapy, Retinal nerve fibre layer, Subfoveal choroidal thickne.

INTRODUCTION

Acne is one of the most common skin inflammatory conditions affecting approximately 9.4% of the world's population.¹ This disease can be associated with anxiety, decreased self-esteem, stigma, and facial scar, which can place a significant burden of disease on patients of all ages, but especially adolescents.^{2,3} According to Canadian, American and European clinical practice guidelines, isotretinoin should be used for management of moderate-severe acne treatment.^{4,6} In general practice, clinicians generally prefer isotretinoin as the first-line treatment for acne treatment.⁷

Isotretinoin has many systemic side effects that could be

seen from mild to serious. As is known, many studies have shown that systemic side effects and costs are more reasonable in low dose isotretinoin treatment than in high dose isotretinoin treatment.^{8,9} Isotretinoin is a synthetic retinoid which is able to affect the growth, differentiation and function of different tissues, and may cause adverse reactions on mucosa, skin, eye, liver, bone, and the musculoskeletal and nervous system.¹⁰ In one study revealed that 3.2% of patients were shown to withdraw from treatment due to the desired side effects including Stevens-Johnson Syndrome, severe cheilitis, severe xerosis, severe acne flare, photosensitivity, elevated liver enzymes, decreased appetite, headache and depressed mood.¹¹

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The most common ocular side effects due to the use of isotretinoin are related with evaporative dry eye developing by meibomian gland dysfunction.¹² However, systemic isotretinoin use related ocular side effects can occur in a wide range from keratitis, induced myopia, papillary edema, optic neuritis, abnormal retinal functions and serous retinal detachment.¹³⁻¹⁵

Evaluation of retinal and choroidal tissues has become easier with the advent of spectral domain optical coherence tomography (SD-OCT) technology. SD-OCT is frequently used in the early diagnosis and follow-up of many systemic drug related ocular toxicity.^{16,17} In this study, we aimed to compare dose-related effect of oral isotretinoin therapy on subfoveal choroidal thickness (SFCT), peripapillary retinal nerve fiber layer (pRNFL) and macular ganglion cell complex (mGCC) layer thicknesses.

MATERIAL AND METHODS

This prospective study followed the tenets of the Declaration of Helsinki and was approved by the local ethics committee. All participants received oral and written information about the study and each participant signed a written informed consent form.

Newly diagnosed moderate to severe nodulocystic acne patients aged between 18-30 years who have not any contraindications to receive isotretinoin treatment were referred from the dermatology department to the ophthalmology department. The patients were treated at doses of 0.5 to 2 mg/kg/d (Roaccutane, Roche). Patients were divided into two groups according to their treatment doses. Group 1 patients were identified as receiving low-dose therapy (<0.5 mg/kg/d), while Group 2 patients were identified as receiving high-dose therapy (> 0.5 mg/kg/d). The total cumulative dose for a full course was 100 to 150 mg/kg. Laboratory tests including blood count, liver enzymes and serum lipids, and pregnancy testing for women were performed before treatment and repeated monthly.

All participants underwent comprehensive ophthalmologic evaluation including best-corrected visual acuity (BCVA), color vision examination with Ishihara cards, pupillary light reactions, intraocular pressure measurement, biomicroscopic anterior segment and dilated fundoscopic examination at the initial visit. After the examinations SD-OCT measurements were performed. All ophthalmic examination and SD-OCT measurements were repeated at fourth month visit and one month after the cessation of treatment.

The inclusion criteria were aged at least 18 y, with no history of any systemic and/or ocular medication use. Further criteria included (1) best-corrected visual acuity (BCVA) of at least 0.8 Snellen, (2) a refractive error (RE) between +3D and -4D, (3) no history of any intraocular surgery and (4) no history of systemic or ocular diseases, such as diabetes mellitus, systemic hypertension, glaucoma or trauma, that could affect the retina and choroid blood flow.

SD-OCT Imaging

All SD-OCT (RS-3000, Nidek) measurements were performed during the same daily interval (10–12 am) by same technician. Only high-quality images (signal strength ≥ 7) that clearly revealed all of the peripapillary and macular regions were retained. The SFCT was measured with enhance depth image (EDI) mode and measurements were manually performed in an area bounded by the outer limit of the retinal pigment epithelium and the inner scleral border by two independent blinded observers. No statistically significant difference in SFCT data yielded by left and right eyes was evident. The mean SFCT value for each patient was obtained by averaging the results from right and left eyes.

Automated measurements of the pRNFL and macular GCC were performed by a built-in software program. The pRNFL thickness was measured by SD-OCT with a 3.46 mm in diameter scan circle centred on the optic disc. This provided the pRNFL thickness values for 4 quadrants (N – nasal, T – temporal, S – superior and I – inferior), 6 sectors (N – nasal, NS – nasal-superior, T – temporal, TS – temporal-superior and NI – nasal-inferior) and global mean values (360 degrees). The mGCC thickness was accepted as between the surface of the internal limiting membrane and the outer boundary of the inner plexiform layer.

Statistical analyses

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. Differences with a value of $p < 0.05$ were considered to be statistically significant.

RESULTS

Sixty two of the 65 patients completed the study. Three patients dropped out of the study: one of them in group 1 and two of them in group 2 had some laboratory abnormalities. There were 42 women and 20 men at 21.17

years mean age (range: 18-39). The age, sex distributions of the two groups were homogeneous, with no statistical differences ($p>0.05$). The mean duration of treatment was 5.40 ± 1.02 months in group 1 and 5.5 ± 1.14 months in group 2 (range 4-7months) ($p=0.77$). Table 1 show the comparison of characteristics and clinical findings of the study groups.

The initial mean SFCT was $285.61 \pm 24.35 \mu\text{m}$ in group 1 and $288.34 \pm 22.18 \mu\text{m}$ in group 2. There was no statistically significant between-group difference in SFCT at baseline ($p=0.79$). At fourth month visit, the mean SFCT was $283.73 \pm 21.45 \mu\text{m}$ in group 1 and $290.42 \pm 21.14 \mu\text{m}$ in group 2 and there was also no statistically significant difference in the two groups ($p= 0.38$). After the cessation of the oral isotretinoin treatment, mean SFCT was found $283.66 \pm 22.70 \mu\text{m}$ in group 1 and $284.56 \pm 19.82 \mu\text{m}$ in group 2 ($p=0.74$).

In evaluation of pRNFL, there was no statistically significant between two groups difference in four pRNFL regions at baseline. At fourth month visit, temporal, and inferior quadrants were significantly lower in group 2 than group 1 ($p=0.022$ and $p=0.043$, respectively). After the treatment cessation, temporal quadrant remained significantly lower in group 2 than group 1. Table 2 shows the pRNFL thicknesses for both groups during the study.

Analyses of mGCC thicknesses, the initial mean mGCC values in group 1 was $81.45 \pm 4.91 \mu\text{m}$ and $82.37 \pm 4.72 \mu\text{m}$ in group 2 and differences between two groups were not statistically different ($p= 0.82$). At fourth month visit, the mean mGCC in group 1 ($81.71 \pm 3.88 \mu\text{m}$) was not different statistically than group 2 ($80.74 \pm 3.91 \mu\text{m}$) ($p=0.23$). After the treatment cessation, mean mGCC in group 1 was $81.22 \pm 3.45 \mu\text{m}$ and mean mGCC in group 2 was $80.87 \pm 4.02 \mu\text{m}$. There was no statistically significant

Table 1: The comparison of characteristics and clinical findings of the study groups.

	Group 1 (n=32)	Group 2 (n=30)	P value
Mean Age (years)	21.02±5.42	22.52±4.03	0.33
Gender			
Female	20 (62.5%)	22 (73.3%)	0.45
Male	12 (37.5%)	8 (26.7%)	0.12
Treatment Duration Time (months)	5.40±1.02	5.5±1.14	0.77

Data are presented as mean ± standard deviation.

Table 2: Comparison of the pRNFL values between two groups during the study.

	Group 1 (n=32)	Group 2 (n=30)	P value
Average pRNFL			
• Baseline	105.25±9.30	104.49±8.60	0.58
• 4th month	104.77±8.82	102.81±7.25	0.55
• After treatment	104.19±8.75	102.09±7.02	0.47
Superior pRNFL			
• Baseline	119.58±5.02	119.12±9.35	0.65
• 4th month	118.88±4.74	117.08±9.24	0.71
• After treatment	118.09±4.92	117.77±8.75	0.70
Inferior pRNFL			
• Baseline	117.04±6.60	114.46±9.22	0.058
• 4th month	116.84±6.27	111.23±8.45	0.041
• After treatment	115.74±6.02	111.03±7.93	0.052
Temporal pRNFL			
• Baseline	91.34±6.05	92.35±5.60	0.72
• 4th month	91.14±5.92	89.18±4.72	0.037
• After treatment	91.12±5.88	89.06±5.03	0.033
Nasal pRNFL			
• Baseline	93.04±7.20	92.04±6.15	0.63
• 4th month	92.23±6.80	90.82±6.21	0.61
• After treatment	91.84±5.78	90.22±5.72	0.58

Data are presented as mean ± standard deviation. Abbreviations: pRNFL: peripapillary retinal nerve fiber layer.

between-group difference in mean mGCC thickness after the treatment cessation ($p=0.37$).

DISCUSSION

In recent study, we evaluated the dose-related systemic isotretinoin effect on SD-OCT parameters. While thinning of some pRNFL quadrants were detected, we did not observe any alteration in SFCT and mGCC thickness in both groups receiving treatment at two different doses.

Previous studies showed that most of the systemic isotretinoin side effects are dose-dependent and they also revealed that as the dose is increased, the frequency of side effects also increased.^{18,19} Lambert et al. reported in an animal study that systemic isotretinoin treatment was associated with a reduction in meibomian gland secretions, ductus and ductulus wall thickening, and periacinar fibrosis.²⁰ Meibomian gland dysfunction triggers the risk of blepharoconjunctivitis and dry eye disease which are the most frequent ocular side effects of the isotretinoin. Cumurcu et al. compared the effects of high- and low-dose isotretinoin treatments on lacrimal functions and blepharoconjunctivitis and they found that eye dryness was related to the dose used, at least during the period of treatment while the rate of conjunctival *S aureus* colonization was unrelated to the dose of isotretinoin.²¹

To the best of our knowledge, this is the first study comparing pRNFL thickness, SFCT and mGCC thickness in patients receiving isotretinoin therapy with different doses. Yavuz et al. evaluated the effect of isotretinoin therapy on peripapillary and subfoveal choroidal thicknesses after three months isotretinoin therapy (with average 30.7 mg/d dose) and while they detected an increase in choroidal thickness in two quadrants, namely temporal and superiotemporal quadrants, they did not detect any change in other areas.²² In our study, we evaluated choroidal thickness in only subfoveal area and we did not find any changes in SFCT in both treatment dose groups during the treatment and after the treatment. Yavuz et al. emphasized that the result they found could be from the systemic vasorelaxant feature of the isotretinoin and the anatomical and cellular difference in the temporal and superior quadrants.²²

The RNFL analyses have been used for glaucoma detecting and screening, other visual pathway disease, including traumatic optic neuropathy, chiasmal lesions, and acute optic neuritis.^{23,24} Prolonged latency in P-100 wave in visual evoked potential test could be observed in patients receiving isotretinoin and a case with optical atrophy and thinning in RNFL is also reported.^{25,26} Therefore, these findings are suggesting that isotretinoin therapy might

affect ganglion cells. Previous studies have been evaluated the alteration of RNFL with systemic isotretinoin therapy. Sekeryapan et al. and Kaptı et al. have not found significant difference in post-treatment RNFL thickness compared with pretreatment values in patients received systemic isotretinoin therapy during average 6 months of follow-up^{27,28}. On the other hand, Ucak et al. and Yilmaz et al. have not found significant difference between pre- and post-treatment mean RNFL thicknesses in their patients received isotretinoin therapy.^{29,30} However, they detected significant decrease in temporal inferior quadrant of RNFL. Similarly, we did not find any significant decrease in pRNFL in patients received lower dose. But in patients received high dose isotretinoin, temporal and inferior quadrants of RNFL decreased with isotretinoin therapy and temporal quadrant remained lower after treatment cessation. Our results suggest that the evaluation of temporal inferior quadrant of RNFL may be important to detect side effects of high dose oral isotretinoin therapy on neuro-retinal issues.

Macular GCC is other ideal locations to evaluate neuronal loss and OCT offers a way to measure the neuronal compartment exclusively. Demirok et al. evaluated the patients who took lower doses of the drug for 12 months to observe the possible toxic effects of the therapy on inner retinal layers, and the authors did not identify any unfavorable effect of the drug on retinal ganglion cells by using SD-OCT. In addition, Ucak et al. and Sekeryapan et al. did not find any alteration in their cohort and they indicated that average 6-month course of systemic isotretinoin therapy seems to have no unfavorable effect on retinal ganglion cells.^{27,29} Similarly, our results were also correlated with these studies, and we did not find any statistically significant change in mGCC thickness in any group receiving treatment at different doses during and after systemic isotretinoin therapy. But in our study, we only evaluated the mGCC layer and we did not analyze other layers of neuro-retina. Yilmaz et al. evaluated the full retinal thickness and GCC thickness in macular region and while they detected thinning in some of the macular areas, they did not detect thinning in the GCC layer.

Our study has some limitations, first, it was a single center study, and the sample size was relatively small. Second, electrophysiological tests, color vision and visual field examinations did not perform to detect pRNFL toxicity. So, there is lack of data on how the toxic of isotretinoin affect the RNFL. Also, long-term and larger studies should be conducted to clarify the toxic effect of high dose isotretinoin treatment on the pRNFL.

In conclusion, we compared the dose related retinal

side effect of systemic isotretinoin therapy. Our results suggested that six-month course of low dose isotretinoin therapy caused no SFCT, mGCC and pRNFL alterations on SD-OCT. However, according to our results, high dose isotretinoin therapy at the same period caused pRNFL thinning while caused no SFCT and mGCC thinning. Therefore, monitoring of pRNFL with SD-OCT can detect toxic effects of the isotretinoin therapy, especially in patients who use high doses and may be useful in the follow-up. However, these findings should be confirmed with larger, long-term studies, which include clinical and electrophysiological findings.

Compliance with Ethical Standards

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Disclosure of potential conflicts of interest: All authors declared that there were no conflicts of interest.

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