ORIGINAL ARTICLE

Structural and Functional Assessment in Patients Treated with Systemic Isotretinoin Using Optical Coherence Tomography and Frequency-Doubling Technology Perimetry

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ABSTRACT

A causal association between central nervous system neuropathy and oral isotretinoin has been reported. In this study we aimed to assess retinal nerve fibre layer (RNFL) thickness and visual field changes in patients treated with systemic isotretinoin. Thirty-nine patients treated with 1 mg/kg daily oral isotretinoin were enrolled in this prospective clinical trial. All patients underwent complete ophthalmologic assessment before treatment, on day 60, and 3 months after completion of treatment. RNFL thickness measurements were performed with Stratus optical coherence tomography. Functional testing included frequency-doubling technology perimetry and Humphrey field analyser. Main outcome measures were average RNFL thicknesses and visual field indices (mean deviation, pattern standard deviation). Measurements of RNFL thickness showed no statistically significant change between the three measurements ($p=0.180$). No statistically significant differences were observed in the frequency-doubling technology indices (mean deviation and pattern standard deviation, $p=0.066$ and $p=0.103$, respectively) and in the Humphrey field analyser indices (mean deviation and pattern standard deviation, $p=0.091$ and $p=0.087$, respectively) at day 60 of treatment or 3 months after the cessation of treatment. In this study of 39 patients, systemic use of isotretinoin (1 mg/kg daily) does not cause a statistically significant change in peripapillary RNFL thickness or visual field findings within the usage period, and within 3 months after cessation.

Keywords: Adverse effect, frequency-doubling technology, isotretinoin, optic nerve, visual field

INTRODUCTION

Isotretinoin is a vitamin A derivate that is used to treat severe recalcitrant nodular acne, acne vulgaris, and severe recalcitrant psoriasis.^{1–4} It may, however, cause adverse reactions to mucosa, skin, eyes, liver, bones, and the musculoskeletal system. Adverse ocular effects are dose related and probably the most frequent adverse reactions of isotretinoin. Abnormal meibomian gland secretions, blepharoconjunctivitis, corneal opacities, decreased dark adaptation, keratitis, papilloedema, decreased colour vision, and

pseudotumor cerebri are all reported side effects of systemic isotretinoin treatment.^{2,5–7}

Previous reports have suggested a causal association between central nervous system neuropathy and oral isotretinoin.^{8–10} The evaluation of the neurophysiological abnormalities of ocular nerve functions of isotretinoin has been reported in only one study, in which an increase in latency P100 had been found in 18% of patients after isotretinoin therapy as determined by visual evoked potentials, but it was not statistically significant.⁹ However, we are unaware of previous studies that attempted to study the

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structural and functional assessment of optic nerve in patients treated with oral isotretinoin.

The purpose of this study is to evaluate retinal nerve fibre layer (RNFL) thickness measured by optical coherence tomography (OCT), and perimetric findings assessed by frequency-doubling technology perimetry (FDT) and Humphrey visual field perimetry (HFA) on patients treated with isotretinoin.

MATERIALS AND METHODS

This prospective case series was undertaken in the Departments of Ophthalmology and Dermatology of Selcuk University of Medicine, Turkey. Thirty-nine patients with severe nodulocystic acne who were intended to be treated with oral isotretinoin (1 mg/kg daily) were included in the study. Those with a history or evidence of ocular disease; spherical refractive error $>\pm 6$ dioptres, astigmatism $>\pm 3$ dioptres; diagnosis of glaucoma or ocular hypertension (intraocular pressure >22 mm Hg); opacities of optic media that could bias functional and structural retinal testing; history of ocular surgery; oral oculo-toxic-neurotoxic drugs or corticosteroid intake; and metabolic, neurologic, vascular, or autoimmune disease and subjects older than 50 years of age were excluded. During the treatment and follow-up periods, those patients with serious systemic or ocular adverse effects were also excluded from the study.

Patients were started on about 1 mg/kg daily isotretinoin by the same dermatologist (H.C.A.). A complete ophthalmologic examination, including best-corrected Snellen visual acuity, slit-lamp examination, ophthalmoscopy through a fully dilated pupil, intraocular pressure (IOP), and visual field examination were performed before the onset of treatment (first visit), on day 60 of treatment (second visit), and 3 months after the cessation of treatment (third visit) in all patients.

Peripapillary RNFL thickness measurements were assessed with Stratus optical coherence tomography (Carl Zeiss Meditec Inc., Dublin, CA, USA) and were performed on all patients by a single masked examiner (H.G.). The fast RNFL algorithm was used to obtain RNFL thickness measurements and average thickness was evaluated. Good scans with signal strength >6 , focused images, and proper centring were included in the analysis. Within a 2-week period after clinical examination, both examinations were performed in the same day and the participants completed the perimetry tests before OCT examination.

Visual field analysis was completed with standard automated perimetry (Humphrey perimetry; Zeiss Humphrey Systems, Dublin, CA, USA; Central 24-2 Full-Threshold, SITA standard program) and with frequency-doubling technology perimetry

(Humphrey Systems; N-30 threshold), by the same individual (H.G.). Perimetric defects were confirmed by at least one repeated examination. Reliability criteria for standard automated perimetry (SAP) and frequency-doubling technology (FDT) tests included false positives, false negatives, and fixation loss responses $<33\%$. Mean deviation (MD) and pattern standard deviation (PSD) values were recorded from both the automated and FDT perimetries.

The right eye of each patient was evaluated for the statistical analysis of RNLF thickness and visual field indices. To compare measurements, Friedman's rank test for k-correlated samples was performed utilizing the statistical package for social sciences 11 program (SPSS Inc., Chicago, IL, USA). A p value <0.05 was considered statistically significant.

The local ethics committee approved this study, which was conducted in accordance with the Declaration of Helsinki. All participants provided informed consent.

RESULTS

The study included 39 eyes of 39 patients (15 men and 24 women; mean age: 22 ± 6.2 years). Treatment had been started at a mean daily dose of 58.6 ± 4.7 mg. The mean duration of treatment with isotretinoin was 5.8 ± 1.9 months, and the mean cumulative dose was 116 ± 31.2 mg/kg.

Ophthalmologic examination, including best-corrected Snellen visual acuity, slit-lamp examination, and ophthalmoscopy through a fully dilated pupil revealed no change at any visit in all patients. There was no significant difference ($p > 0.244$) in IOP between pretreatment, on day 60 of treatment, or after treatment (12.51 ± 4.01 , 13.82 ± 3.31 , and 13.11 ± 3.87 mm Hg, respectively). Average RNFL thickness measurements showed no statistically significant change between the three measurements ($p > 0.180$; Table 1). The MD and PSD values recorded by SAP and FDT perimetry had no statistically significant change after 60 days of treatment or 3 months after cessation of treatment (Table 1).

DISCUSSION

Retinoids are thought to play an essential role in the growth, differentiation, and function of nervous tissue in vivo and in vitro.¹¹ Several studies have been reported that retinoids may be capable of affecting central nervous system.⁸⁻¹⁰ Decreased visual acuity, various visual field defects, pseudotumor cerebri, and optic neuritis are the most common side effects involving the ocular nervous system, which is a part of central nervous system that are definitely or probably related to oral isotretinoin therapy.^{1,2,12-14}

TABLE 1 Mean values of retinal nerve layer fibre thickness, and mean deviation and pattern standard deviation values for both frequency-doubling technology perimetry and standard automated perimetry before, at days 60 of, and after the treatment.

Measurement	Pretreatment	At days 60 of treatment	3 months after the cessation of treatment	<i>p</i> value
RNFL Thickness	103.63 ± 5.1	99.41 ± 7.3	102.74 ± 6.9	0.180
FDT MD (dB)	0.48 ± 1.27	0.36 ± 1.67	0.29 ± 2.01	0.066
FDT PSD (dB)	3.44 ± 2.62	2.55 ± 1.14	2.67 ± 1.88	0.103
SAP MD (dB)	-1.66 ± 2.73	-0.92 ± 1.59	-1.81 ± 3.11	0.091
SAP PSD (dB)	2.99 ± 2.58	2.61 ± 0.77	2.27 ± 1.18	0.087

RNFL = retinal nerve fibre layer; FDT = frequency-doubling technology; SAP = standard automated perimetry; MD = mean deviation; PSD = pattern standard deviation; dB = decibel.

The optic nerve is composed of retinal ganglion cell axons and is responsible for carrying optic impulses from the retina to the optic chiasm. Loss of retinal ganglion cells and RNFL would be reflected in reduction of the retinal thickness. Several studies have reported the importance of RNFL thickness determination in the early diagnosis and management of optic nerve conditions such as glaucoma and optic nerve diseases including optic neuritis.¹⁵ Optical coherence tomography can reveal changes in RNFL thickness before visual field defects appear. Dinc *et al.* have reported a case of bilateral optic nerve atrophy associated with decreased RNFL thickness, and suggested a relation between isotretinoin treatment and the ocular findings.¹⁶ However, that case had a brain lesion that was probably related with her preterm status. Therefore, optic atrophy and RNFL thinning were likely the results of coexisting brain defect in that case. Although mean daily dose of isotretinoin is higher in our patients than this case with bilateral optic atrophy, we found no statistically significant change in RNFL measurements among the three measurements ($p > 0.180$).

Visual field testing is most frequently used to detect glaucoma or diseases affecting the optic nerve, retina, and visual pathways within the brain. Any toxic effect on the optic nerve may result in various visual field defects, including central and/or paracentral scotoma.¹⁷ Standard automated perimetry is the current gold standard for assessing visual function in optic nerve diseases. Studies have shown, however, that patients can lose up to 40% of retinal ganglion cells before developing visual field defects detectable by SAP.¹⁸ Therefore, we also evaluated optic nerve functions by FDT perimetry, which measures contrast sensitivity and selectively tests the function of the M_y subset of M ganglion cells. We found no statistical difference between the MD and PSD values recorded by standard automated and FDT perimetries during or after the cessation of treatment. Since optic nerve fibres, thus visual field testing, can be affected by elevated IOP, we included IOP readings of our patients in all visits and found no difference at any time during the study ($p > 0.244$).

It is unclear how isotretinoin could produce nervous system dysfunction, but several possible mechanisms exist. All-*trans*-retinoic acid is known to regulate development, proliferation, differentiation, and function of a variety of cell lines, including neural precursors and the anteroposterior pattern in of the central nervous system (CNS).¹¹ Regarding the effect of retinoids of the CNS, Aydogan *et al.* suggested a metabolic, rather than toxic, mechanism to explain nerve conduction abnormalities in their patients.⁹ Another mechanism regarding the nervous system is described by Le Coz *et al.*, who believe that pathogenesis involves changes in the lipid composition of nerve cell membranes.¹⁰

Since visual evoked potential (VEP) measures the function of visual pathways, the clinical findings regarding structural and functional assessment in our patients should have been confirmed electrophysiologically. In a recent study, increased latency of the P100 wave was detected after therapy in 18% of patients treated orally with isotretinoin, although this was not statistically significant.⁹ It may be possible that there are subclinical effects of isotretinoin on structural and functional results, which can be detected electrophysiologically, before clinical signs occur. Because our patients did not have any neurological complaints, no correlation could be made between the structural and functional findings and patient complaints. However, among these asymptomatic patients, we found no subclinical changes within the usage period. It is possible that OCT and visual field tests can be used in screening for possible changes in symptomatic patients. Another limitation of this study is the small size of our study population, and the short time period of follow-up. Further studies should be performed to identify the long-term quantitative and qualitative effects of isotretinoin on ocular neurotoxicity.

In conclusion, this paper represents the first study evaluating RNFL thickness and perimetric findings in response to oral isotretinoin. Our study with limited number of patients demonstrates that oral isotretinoin treatment does not affect peripapillary RNFL thickness or visual field within the usage period and within 3 months after cessation, in our 39 patients.

However, these findings should be confirmed with larger, randomized, long-term studies, which include clinical and electrophysiological findings.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

- [1] Brelsford M, Beute TC. Preventing and managing the side effects of isotretinoin. *Semin Cutan Med Surg* 2008;27: 197–206.
- [2] Ellis CN, Krach KJ. Uses and complications of isotretinoin therapy. *J Am Acad Dermatol* 2001;45:S150–S157.
- [3] Fraunfelder FT, Fraunfelder FW, Edwards R. Ocular side effects possibly associated with isotretinoin usage. *Am J Ophthalmol* 2001;132:299–305.
- [4] Santaella RM, Fraunfelder FW. Ocular adverse effects associated with systemic medications: recognition and management. *Drugs* 2007;67:75–93.
- [5] Bozkurt B, Irkec MT, Atakan N, Orhan M, Geyik PO. Lacrimal function and ocular complications in patients treated with systemic isotretinoin. *Eur J Ophthalmol* 2002; 12:173–176.
- [6] Santodomingo-Rubido J, Barrado-Navascues E, Rubido-Crespo MJ. Drug-induced ocular side-effects with isotretinoin. *Ophthalmic Physiol Opt* 2008;28:497–501.
- [7] Fraunfelder FW. Ocular side effects associated with isotretinoin. *Drugs Today (Barc)* 2004;40:23–27.
- [8] Nikiforidis G, Tsambaos D, Karamitsos D, Koutsojannis C, Georgiou S. Effects of oral isotretinoin on human auditory brainstem response. *Dermatology* 1994;189: 62–64.
- [9] Aydogan K, Turan OF, Onart S, Yazici B, Karadogan SK, Tokgoz N. Neurological and neurophysiological effects of oral isotretinoin: a prospective investigation using auditory and visual evoked potentials. *Eur J Dermatol* 2008;18: 642–646.
- [10] Le Coz CJ, Wasser P, Tranchant C, Cribier B, Heid E, Warter JM, Grosshans E. Abnormal central nervous conduction in long-term treatments with retinoids. *Ann Dermatol Venereol* 1996;123:795–799.
- [11] McCaffery P, Drager UC. Regulation of retinoic acid signaling in the embryonic nervous system: a master differentiation factor. *Cytokine Growth Factor Rev* 2000;11: 233–249.
- [12] Fraunfelder FT, LaBraico JM, Meyer SM. Adverse ocular reactions possibly associated with isotretinoin. *Am J Ophthalmol* 1985;100:534–537.
- [13] Fraunfelder FW, Fraunfelder FT, Corbett JJ. Isotretinoin-associated intracranial hypertension. *Ophthalmology* 2004; 111:1248–1250.
- [14] Lee AG. Pseudotumor cerebri after treatment with tetracycline and isotretinoin for acne. *Cutis* 1995;55:165–168.
- [15] Pinilla I, Garcia-Martin E, Idoipe M, Sancho E, Fuertes I. Comparison of retinal nerve fiber layer thickness measurements in healthy subjects using fourier and time domain optical coherence tomography. *J Ophthalmol* 2012; 2012:107053.
- [16] Dinc UA, Yenerel NM, Gorgun E, Oral D, Oncel B, Oncel M. A case with bilateral optic nerve atrophy associated with isotretinoin treatment for acne vulgaris. *Neuro-ophthalmology* 2007;31:49.
- [17] Riordan-Eva P. Clinical assessment of optic nerve disorders. *Eye (Lond)* 2004;18:1161–1168.
- [18] Quigley HA, Dunkelberger GR, Green WR. Retinal ganglion cell atrophy correlated with automated perimetry in human eyes with glaucoma. *Am J Ophthalmol* 1989;107: 453–464.