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Change in the Thickness of Retinal Layers after Selective Retina Therapy (SRT) in Patients with Central Serous Chorioretinopathy

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Abstract

Background

To investigate retinal thickness after selective retina therapy (SRT) for central serous chorioretinopathy (CSC) and the factors related to visual prognosis.

Methods

This retrospective study examined 23 eyes of 21 consecutive patients (17 males, 4 females) with CSC and followed-up for >6 months. A SRT (Q-switched Nd:YLF laser, 527 μm, pulse duration 1.7 μs, 30 pulses per irradiation spot with a frequency of 100 Hz) was used for the treatment. The need for re-treatment was judged every three months after the initial treatment. The best corrected visual acuity (BCVA) and central macular thickness (CMT) were compared among pre-treatment, at the time of resolution, and at final follow-up examination. Furthermore, the inner retinal thickness (IRT) and outer retinal thickness (ORT) at the time of resolution and at final follow-up, and their rates of change were also investigated.

Results

Final BCVA improved (logMAR: from 0.01±0.22 to −0.10±0.15) and the CMT decreased (from 336±78 μm to 185±28 μm) significantly after SRT compared with pre-treatment. The IRT did not change from the time at resolution to the final examination, while the ORT increased significantly during this time period (from 77±11 μm to 86±10 μm). A stepwise regression analysis identified that the pre-treatment BCVA and the rate of ORT increase have a significant positive correlation with the final BCVA.

Conclusions

SRT may improve final visual acuity of the patient of CSC, which is accompanied by the increase in the thickness of the outer retinal layer shortly after the resolution of subretinal fluid.

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Key Words: Laser therapy; Central serous chorioretinopathy; Retina; Subretinal fluid

Introduction

Central serous chorioretinopathy (CSC) is accompanied by subretinal fluid (SRF) of the macular region, and can lead to reduced visual acuity, metamorphopsia, micropsia, central scotoma, and decreased contrast sensitivity, etc[1,2]. It is a disease that can be expected to resolve spontaneously within a few months, with a good prognosis for visual acuity. However, there are some cases in which SRF is long-standing, which often develop irreversible damage to the neurosensory retina and retinal pigment epithelium (RPE), sometimes with permanent sequelae[3-5].

Selective retina therapy (SRT) was developed as a laser procedure in which the RPE cells are selectively disrupted without affecting the neural retina or choroid[6-8]. In this procedure, a microsecond pulsed laser is used to induce an instantaneous increase in the temperature of just at the melanosomes in the RPE. When exceeding the vaporization temperature microbubbles around the melanosomes occur, resulting in a temporary expansion of the volume of the cells that causes mechanical disruption of the RPE cells. Due to the spatial and temporal thermal confinement through the laser pulse shorter than the thermal relaxation time of the RPE, there is no significant temperature increase in the surrounding tissues which might cause thermal damage[9,10].

SRT is known to be effective for CSC, diabetic macular edema (DME), and prolonged SRF after retinal detachment[11-17]. The therapeutic mechanism of SRT is to disrupt diseased RPE cells and promote the regrowth of the surrounding healthy ones. We previously reported the safety of SRT for CSC using microperimetry up to 3 months after treatment[17]. Although it is known that SRT is effective in the short term to resolve subretinal fluid for CSC, there has been no study on the factors related to visual acuity after SRT. The current study aimed to observe the retinal thickness after SRT in detail and to investigate factors related to visual prognosis.

Methods

This retrospective study examined 23 eyes of 21 consecutive patients (17 males, 4 females) diagnosed with CSC and followed-up for more than 6 months at Osaka City University Hospital during the study period from July 2011 to July 2013. The average patient age was 48.1 years (range, 29 to 67 years). The basic clinical data of all patients are shown in Table 1.

The inclusion criteria were as follows: (1) minimum age of 20 years; (2) subjective symptoms of central scotoma, metamorphopsia, or decline of visual acuity; (3) history of more than 3 months with no sign of improvement of CSC [diagnosed with optical coherence tomography (OCT)]; (4) presence of SRF on OCT; (5) presence of active leakage on fluorescence angiography (FA); and (6) SRF disappeared within 1 year after the last SRT, and no recurrence occurred for more than 3 months after resolution of SRF.

The exclusion criteria were as follows: (1) having another retinal disease; (2) having a condition associated with choroidal neovascularization; (3) prior history of another therapy such as PDT or local retinal photocoagulation within the past 6 months; (4) having a systemic inflammatory disease; (5) haemorrhagic diathesis or taking anticoagulants; (6) having a systemic disease such as untreated hypertension or diabetes mellitus; or (7) pregnant or possibly pregnant.

SRT laser

This study was approved by the Institutional Review Board (IRB) of the University hospital (No.

Table 1. Patient characteristics before treatment

Characteristics	
Number of patients	21 Cases (23 eyes)
Sex (Cases; eyes)	Male 17; 19, Female 4; 4
Age; Mean (Range)	48.1 (29-67)
Number of episodes (%)	
First	13 (56.5)
Second or more	10 (43.5)
Characteristics of leakage in FA (%)	
Focal leakage	18 (78.3)
Diffuse leakage	5 (21.7)
Duration of symptom (months); Median (Range)	6 (3-24)
Pretreatment BCVA (logMAR); Mean (Range)	0.03 (−0.30-0.70)
Pretreatment CMT (μm); Mean (Range)	336.0 (226-475)

FA, fluorescein angiography; BCVA, best corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; and CMT, central macular thickness.

2009 and 2421), based on the Declaration of Helsinki, and was registered with University Hospital Medical Information Network (UMIN) (No. 000005396). Written informed consent was acquired from all patients. The SRT laser system used was developed by the Medical Laser Center Lübeck (Lübeck, Germany). The laser itself is a Q-switched Nd:YLF-laser (wavelength 527 nm) with a pulse duration of 1.7 μs, which applies 30 pulses per irradiation spot with a frequency of 100 Hz. A Mainster central field contact lens with a magnifying power of 1.05 was used and adjusted so that the spot size on the retina is 200 μm.

The induced thermomechanical cell damage is not ophthalmoscopically visible during SRT, therefore the generation of microbubbles in the RPE cells and the subsequent RPE cell destruction were inferred from the ultrasonic wave being induced from the microbubble expansion. These ultrasonic waves were measured with a transducer embedded in the contact lens. This signal was processed by a software algorithm to compute an optoacoustic value (OA value) as reported earlier by Yasui et al[17], which serves as an indicator for microbubble formation and thus cell disruption.

After performing visual acuity testing, slit-lamp microscopy, OCT, and fundus autofluorescence, test irradiations were conducted around vascular arcades upper or lower part of the macula in order to decide the range of treatment laser energy. The test irradiation was performed with the energy started at 60 μJ, followed by increases with 20-μJ increments, until the OA value reached several hundred. After test irradiations, FA and Indocyanine Green Angiography (IA) were performed, and leakage from the test irradiation sites was confirmed. The main laser treatment was initiated with the lowest energy level at which leakage was observed in test irradiation. If the OA value is low during treatment, the treatment energy was adjusted such that the OA value might be around several hundred. Following the main treatment, FA was repeated, and after confirming the increase of fluorescein leaks from the treated region, the treatment was concluded.

The need for re-treatment was judged every three months after the initial treatment. If OCT showed residual SRF in the macular region, FA was conducted, and the presence or absence of

fluorescein leaks was confirmed. If fluorescein leaks were present, the leakage site was irradiated with intervals of 2 to 3 spots' diameter, whereas the SRF region was diffusely irradiated in the same manner if no clear leakage points were observed.

Clinical examinations

Best corrected visual acuity (BCVA) and central macular thickness (CMT) were compared among three points in time; before treatment, at the time of resolution, and at the final follow-up examination. The resolution time was defined as the complete disappearance of the SRF on OCT. The time point of the final follow-up examination was at least 3 months after SRF resolution. As for BCVA, decimal visual acuity was measured and converted to logarithm of the minimum angle of resolution (logMAR) for analysis. CMT, defined as the thickness of the retina in the central area, was measured by OCT using a Heidelberg SPECTRALIS® (Heidelberg Engineering GmbH, Heidelberg, Germany). On the OCT images from the time of resolution and final follow-up, the installed image processing software was used to carry out intraretinal segmentation by dividing the retina into two layers, an inner layer and an outer layer, with the external limiting membrane as the dividing line, and their thickness were then compared. The associations between final BCVA and sex, age, recurrent or de novo CSC, time period of subjective symptoms, time required for resolution, visual acuity, and CMT as pretreatment factors, and with inner retinal thickness (IRT) and outer retinal thickness (ORT) at the time of resolution and at final follow-up and their rates of change as post-treatment factors were investigated (Fig. 1). Factors for which $p<0.20$ on single correlation analysis were entered into multivariate analysis by stepwise regression analysis.

Statistical analysis

Differences in BCVA were tested using Wilcoxon's signed-rank test for significance, and differences

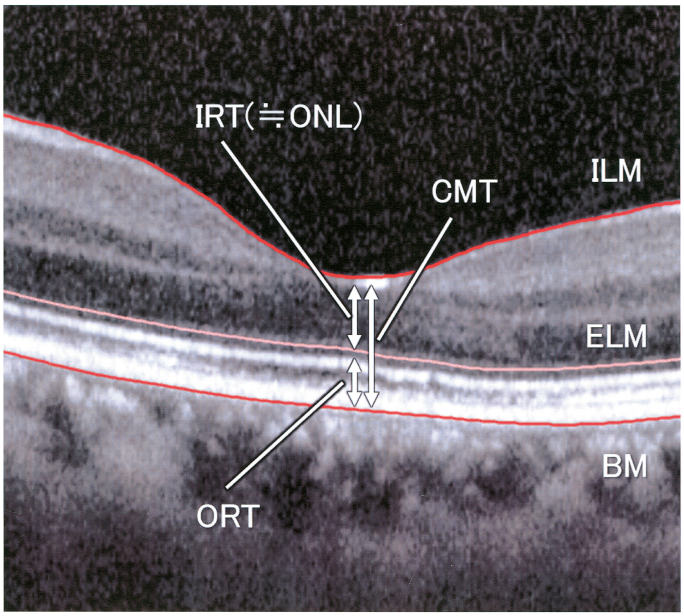

Figure 1. A horizontal scan of spectral domain optic coherence tomography (SD-OCT) through the central fovea. Central macular thickness (CMT) is defined as the distance between the surface of the inner limiting membrane (ILM) and the inner border of the Bruch's membrane (BM) at the central fovea. Inner retinal thickness (IRT) is measured as the distance between the outer border of the ILM and the inner border of the external limiting membrane (ELM). IRT is almost the same as outer nuclear layer (ONL) at fovea. Outer retinal thickness (ORT) is measured as the distance between the outer border of the ELM and the inner border of the BM.

in CMT, IRT, and ORT were tested using a paired t-test. Correlations were investigated using Pearson's correlation coefficient for pairs of normally distributed variables and Spearman's rank correlation coefficient for non-normally distributed variables. Associations with sex and recurrence status were tested using the Mann-Whitney U test. When comparing three groups, a paired t-test was performed for every pair of group, and the p values were adjusted using the False Discovery Rate method. The statistical software used was IBM® SPSS® Statistics 24.0 (IBM Japan, Ltd., Tokyo, Japan), and $p<0.05$ was regarded as significant.

Results

The number of test irradiations required for initial treatment ranged from 4-12 (mean 7.8), and the number of irradiations required for the main laser treatment ranged from 2-17 (mean 7.0). The irradiation energy used in initial treatment ranged from 62-184 μJ (median 116 μJ), and the OA value was 54-6455 (median 225). The number of SRT sessions required until SRF resolution was 1-3 (mean 1.3). The time from initial treatment to resolution was 1-12 months (median 1 month), and the time from resolution to final follow-up was 3-6 months (median 4 months). A representative case of CSC is shown in Figure 2.

Mean BCVA (logMAR) was 0.01±0.22 pre-treatment, −0.04±0.20 at the time of resolution, and −0.10±0.15 at final follow-up, with significant differences between the values at final follow-up and

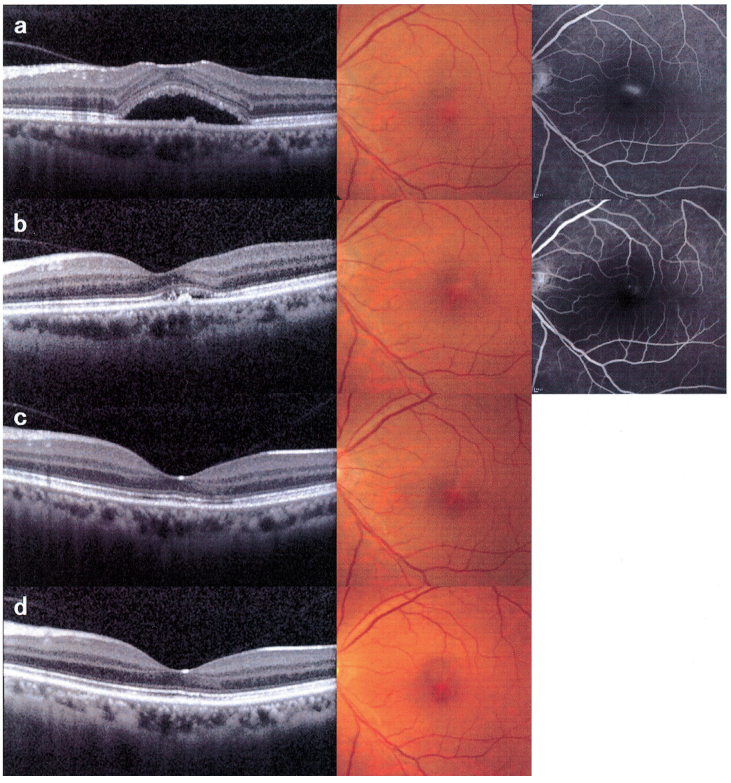

Figure 2. A representative case of central serous chorioretinopathy (CSC). Horizontal scan of optic coherence tomography (OCT) (left), color fundus image (center) and fluorescein angiography (FA) (right) of pretreatment (a), 3 months after SRT (b), resolution of SRF at 6 month (c), and final follow-up (at 12 month) (d). Subretinal fluid (SRF) decreased and the leakage on FA disappeared at 3 months follow-up after SRT (b), followed by the SRF disappearance at 6 months (c). At 12 months follow-up after SRT, there is no recurrence, and the outer retinal thickness was increased from 77 μm to 86 μm (d).

those both pre-treatment and at the time of resolution (pre-treatment vs final follow-up $p<0.01$, resolution vs final follow-up $p<0.01$) (Fig. 3).

Mean CMT was 336±78 μm pre-treatment, 175±25 μm at resolution, and 185±28 μm at final follow-up, with significant differences between all three time points (pretreatment vs resolution, $p<0.001$; pretreatment vs final follow-up, $p<0.001$; resolution vs final follow-up, $p<0.001$) (Fig. 4). There was no significant difference between IRT during at resolution (97±21 μm) and at final follow-up (98±24 μm; $p=0.45$), whereas ORT showed a significant increase, where it was 77±11 μm at resolution and 86±10 μm at final follow-up ($p<0.001$) (Fig. 5).

Single correlation analysis identified pre-treatment BCVA, IRT at resolution, and the rates of change of IRT and ORT between at resolution and at final examination as significant factors

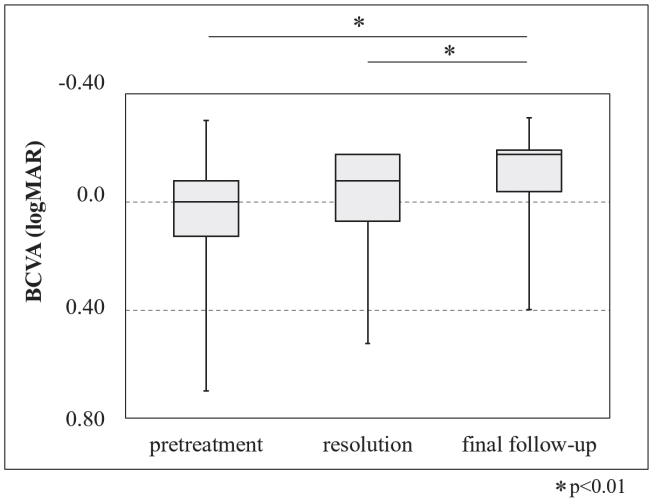

Figure 3. Box plots for the time course of best corrected visual acuity (BCVA) (logMAR). Mean BCVA was 0.01±0.22 pre-treatment, −0.04±0.20 at the time of resolution, and −0.10±0.15 at final follow-up, with significant improvement between each time point toward the final follow-up.

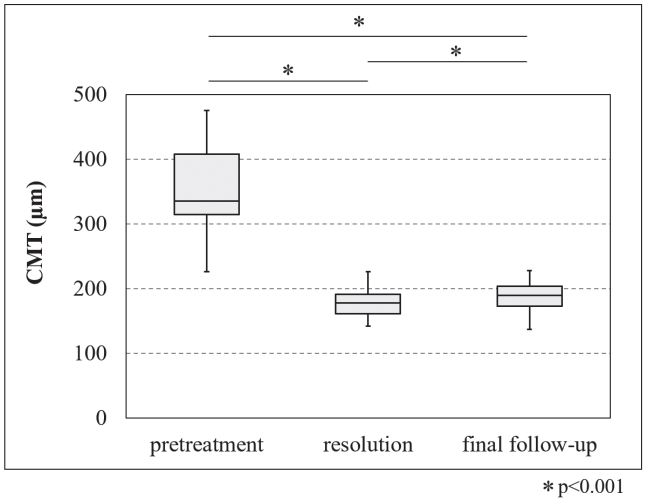

Figure 4. Box plots for the time course of central macular thickness (CMT). Mean CMT was 336±78 μm pre-treatment, 175±25 μm at resolution, and 185±28 μm at final follow-up, with significant differences between all three time points.

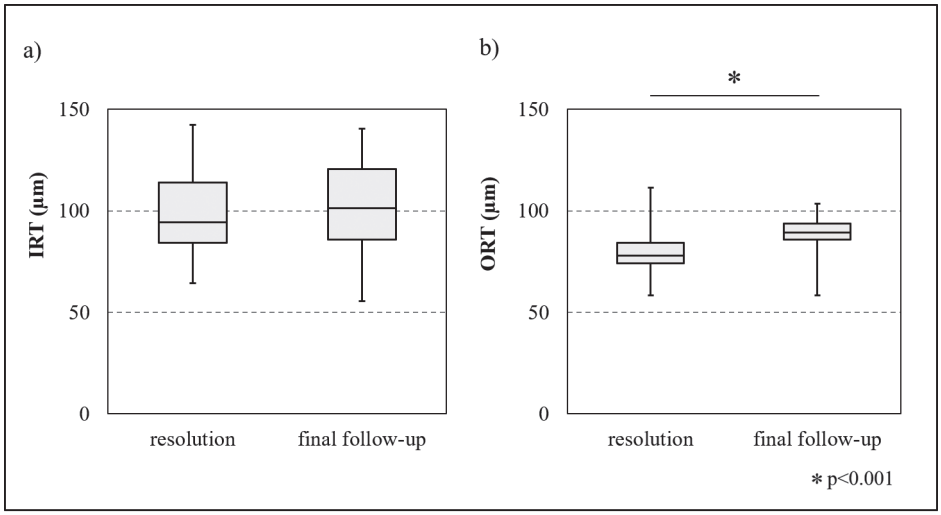

Figure 5. Box plots for the time course of inner retinal thickness (IRT) (a) and outer retinal thickness (ORT) (b). There was no significant difference of IRT between at the time of resolution (97±21 μm) and at final follow-up (98±24 μm), whereas ORT showed a significant difference, where it was 77±11 μm at the time of resolution and 86±10 μm at final follow-up.

Table 2. Univariate analysis of factors associated with final BCVA

variables	r, ρ	p value
Pretreatment		
Sex*1	-	0.50
Age*2	0.07	0.75
Recurrence*1	-	0.87
Duration of symptom*2	0.09	0.69
Pretreatment BCVA*3	0.84	<0.001
Pretreatment CMT*3	−0.283	0.19
Resolution		
Disappearance time of SRF*2	0.23	0.30
Inner retinal thickness*3	−0.45	0.03
Outer retinal thickness*3	−0.39	0.07
Final follow-up		
Δ Inner retinal thickness*3	−0.44	0.03
Δ Outer retinal thickness*3	−0.63	<0.001

*1: Mann-Whitney U test. *2: Spearman's rank correlation coefficient. *3: Pearson's correlation coefficient. BCVA, best corrected visual acuity; CMT, central macular thickness; and SRF, subretinal fluid.

Table 3. Multivariate analysis of factors associated with final BCVA

variables	B	SE B	β	p value
BCVA	0.49	0.12	0.66	0.01
Δ Outer retinal thickness	−0.75	0.31	−0.37	0.03
R^2 0.78				

SE, standard error; and BCVA, best corrected visual acuity.

associated with final BCVA (Table 2). Stepwise regression analysis of factors for which $p<0.20$ identified significant associations with pre-treatment BCVA and the rate of change of ORT (Table 3).

Discussion

The persistence of SRF is known to cause structural changes in the neuroretina and RPE that undoubtedly affect the prognosis for visual acuity. Atrophy of the subfoveal RPE and cystoid macular degeneration have been implicated in causing the serious loss of vision that occurs in chronic CSC[1,2]. However, more than that, the thickness of the outer nuclear layer (ONL) after resolution of SRF is also considered to be one of the important determining factors for visual prognosis[18,19]. When SRF persists long-term, extension of the photoreceptor outer segment and thinning of the ONL are known to occur[20,21]. Regarding the retina of the patients with resolved CSC, Nakamura et al reported that the cone density (cell density in the ONL) measured with adaptive optics fundus camera is significantly decreased, which is associated with the decrease of the ORT and visual acuity[22]. In cases of protracted SRF treated by photo dynamic therapy (PDT), the thickening of the ONL after treatment is reportedly positively associated with the better visual prognosis after SRF resolution[18,19,23,24]. These changes after SRF resolution following PDT include the improvement of the visibility of the ellipsoid zone and the ONL increasing in thickness. In the present study, IRT, which is almost the same as the range of the ONL at fovea, did not change significantly during post-resolution follow-up, but the ORT increased significantly. In the detailed correlation analysis it was also shown that the thickness increase of the ORT after treatment is positively correlated to the visual prognosis, not of the IRT, which is not consistent with the previous reports. As the reason of it, some possibility can be discussed; First, it might be just because the short observation period in this study. Secondly, it may lie on the difference in the therapeutic mechanism between PDT and SRT. Namely, it would be hypothesized that SRT might promote the restoration of photoreceptors outer segment (the main component of the ORT), better or at least earlier, than after PDT. However, as there are still no comparison studies, further investigation is necessary to evaluate the changes in retinal thickness after different therapies.

The limitations of this study include its nature as a retrospective study, its small sample size, the comparatively short follow-up period of 3-6 months after SRF resolution, and the fact that patients with recurrent or persistent SRF were excluded. If patients can be maintained long-term without SRF recurrence, further changes in retinal structure might occur. The effect of recurrent or persistent SRF must also be taken into account in the case of long-term follow-up.

In conclusion, SRT may improve final visual acuity significantly, and this improvement was associated with two factors: pretreatment visual acuity and the rate of change in ORT. Although CSC is a disease with a high tendency to heal spontaneously, the persistent SRF can cause the morphological changes in the neuroretina as well as of the RPE, which has been shown to associate with the decreasing visual acuity. Therefore, its earlier resolution needs to be prioritized to preserve the retinal structure and the long-term visual acuity of patients with CSC.

Acknowledgments

All authors have no COI to declare regarding the present study.

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