Selective retina therapy with real-time feedback-controlled technology in central serous chorioretinopathy: a 24-month follow-up real-world prospective study

Chang Ki Yoon, Hyeong Gon Yu

INTRODUCTION

Central serous chorioretinopathy (CSC) is a chorioretinal disease characterised by the detachment of the central area of the neurosensory retina, accompanied by the presence of subretinal fluid (SRF). Various treatments for CSC have been reported, including intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF), conventional focal laser photocoagulation, photodynamic therapy (PDT), subthreshold laser treatment and oral administration of mineralocorticoid receptor antagonists. However, a standardised treatment modality has not yet been established owing to the risk of adverse events and controversies regarding treatment efficacy. Although anti-VEGF therapy has been explored as a CSC treatment, it is financially burdensome and has questionable efficacy. Considering the association between CSC and choroidal vessel hyperpermeability, PDT using verteporfin is a recommended treatment with favourable clinical outcomes; however, it presents drawbacks such as high costs, systemic side effects and retinal pigment epithelium (RPE) atrophy. Eplerenone, a mineralocorticoid receptor antagonist, failed to show efficacy in the double-blind, randomised, placebo-controlled VICI trial. Direct focal laser photocoagulation has been used for CSC for many years, yet the risk of scotoma and choroidal neovascularisation makes such treatment less favoured.

To avoid photoreceptor damage, subthreshold micropulse laser (SMPL) and...
Selective retinal therapy (SRT) have been introduced as alternative approaches to conventional photocoagulation lasers. SMPL, using a pulse duration of 100–300 μs, involves a possible risk of undertreatment, even though it can effectively treat CSC without significant impairment of retinal function or adverse events.9 10 Employing much shorter laser pulses in several microseconds, SRT selectively targets RPE cells through a combination of thermal and thermomechanical effects without damaging the adjacent RPE or neurosensory retina.11 12 However, as the treatment response is not visible, real-time feedback (RTF) technology using optoaoustic–reflectometric feedback signals has been introduced to ensure the therapeutic effects of SRT.13 14 The safety and efficacy of SRT with RTF technology has been demonstrated in various clinical conditions, including chronic and acute CSC.15–18

In a recent study, SRT with RTF showed favourable treatment outcomes in patients with bevacizumab-resistant chronic CSC.19 Since recurrent and chronic CSC leading to visual impairment are common conditions, observational studies with longer follow-up periods are warranted. Herein, we aimed to evaluate the safety and efficacy of SRT for CSC treatment with a follow-up period of up to 24 months in a real-world clinical setting.

**MATERIALS AND METHODS**

**Study participants**

This prospective, real-world study was conducted as requested by the Korean Center for New Health Technology Assessment (NECA, Korean Ministry of Health and Welfare) to assess SRT for CSC as part of a limited medical technology evaluation programme.

We intended to recruit 50 patients with CSC and SRF involving the fovea, aged between 19 and 55 years. Symptom duration was not restricted in this study. Patients were excluded if they presented other retinal diseases, such as choroidal neovascularisation, polypoidal choroidal vasculopathy or media opacity, which makes laser treatment difficult and ineffective. Additionally, patients who were participating in other intervention research or did not provide written informed consent were excluded from the study.

**SRT procedure**

SRT was performed using an SRT laser system (R:GEN, Lutronic Corporation, Goyang, South Korea) equipped with a Q-switched neodymium-doped yttrium lithium fluoride (Nd:YLF) 527 nm laser (pulse duration, 1.7 μs; spot size, 200 μm; repetition rate, 100 Hz; and energy range, 30–350 μJ) and an RTF system using RTF sensors. The RTF technology uses a maximum burst of 15 micropulses at 100 Hz for each SRT spot, with the energy of each micropulse being ramped up linearly so that the first micropulse energy is equal to 50% of the energy of the 15th micropulse. In the middle of the 15-micropulse train, the system stops to irradiate when adequate energy for treatment is detected using an RTF system. Before applying the laser to the targeted area, test shots were performed to determine the proper preset pulse energy of the 15th pulse. Detailed information on ways to perform the test shots was described previously.15 During a treatment session, the surgeon could change the preset energy if the system detected signs of undertreatment or overtreatment. Multiple SRT spots with a distance of 0.5–1 spot size were applied surrounding and above each leakage area, which was determined based on fluorescein angiography (FA) screening. The positions of the test and treatment shots are demonstrated as dotted green and orange circles, respectively, overlaid on an FA image in online supplemental figure 1. During the follow-up period, concomitant treatments were performed if the SRF was persistent or recurrent and the CSC symptoms were not resolved. The need for concomitant treatments was determined by the principal investigator to simulate real-world clinical practice settings.

**Treatment outcome measures**

At the screening visit, a full ophthalmological examination, including a best-corrected visual acuity (BCVA) test, colour fundus photography, slit-lamp biomicroscopy, fundus autofluorescence, FA and optical coherence tomography (OCT), was performed on each patient. The BCVA was determined using a standard Snellen chart and converted to the logarithm of the minimum angle of resolution (logMAR). OCT was performed using a spectral-domain OCT system (Heidelberg Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany). The same ophthalmological examinations were repeated

### Table 1: Outcomes 6 months after treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Value, mean±SD</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA (logMAR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.15±0.18</td>
<td>–</td>
</tr>
<tr>
<td>1 month</td>
<td>0.14±0.18</td>
<td>0.251</td>
</tr>
<tr>
<td>3 months</td>
<td>0.11±0.17</td>
<td>0.017</td>
</tr>
<tr>
<td>6 months</td>
<td>0.12±0.21</td>
<td>0.062</td>
</tr>
<tr>
<td>CRT (μm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>350.6±100.1</td>
<td>–</td>
</tr>
<tr>
<td>1 month</td>
<td>276.6±78.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 months</td>
<td>269.6±65.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 months</td>
<td>268.2±70.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak SRF height (μm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>152.1±86.1</td>
<td>–</td>
</tr>
<tr>
<td>1 month</td>
<td>81.9±80.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 months</td>
<td>67.5±67.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 months</td>
<td>63.4±76.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P value for Wilcoxon signed-rank test (or paired sample t-test) to compare each post-treatment visit and the baseline.

BCVA, best-corrected visual acuity; CRT, central retinal thickness; logMAR, logarithm of the minimum angle of resolution; SRF, subretinal fluid.
at follow-up visits every 3 months from the treatment. The central retinal thickness (CRT) was estimated using the OCT system software (Heidelberg Engineering, Heidelberg, Germany), and the peak SRF height was determined as the highest SRF height of all OCT B scans. Complete SRF resolution was determined as the absence of SRF in all OCT B scans. The correlation between various factors and outcomes, such as symptom duration and BCVA and peak SRF height changes, was examined. A primary evaluation was conducted for the 6-month follow-up of all treatment outcomes, and long-term evaluation was conducted for the 24-month follow-up data of CRT, SRF resolution and BCVA outcomes.

Statistical analysis
Efficacy evaluation was performed for patients who underwent SRT and completed at least one follow-up visit, whereas the safety analysis was conducted on all study participants who received at least one SRT. For the efficacy evaluation, descriptive statistics for the outcomes were noted and analysed. A paired sample t-test or Wilcoxon signed-rank test was used to confirm significant differences in each outcome at different visits. The Wilcoxon rank-sum or two-sample t-test was used to validate the difference in treatment outcomes between the concomitantly treated and SRT-only treated groups. Linear regression analysis was performed to examine the correlation between symptom duration and clinical outcomes and between BCVA and peak SRF height changes. All statistical tests were two tailed, and p < 0.05 were considered significant. In this study, missing values were imputed using the last observation carried forward method if data were available within 6 months; for the long-term evaluation, patients without data at a specific time point were excluded from the analyses. For each patient, the data acquired at the last follow-up visit were considered as the last visit data.

Statistical analysis was performed using the SAS software (V.9.4).

Patient and public involvement
Patients or the public were not involved in the design, conduction, reporting or plans to disseminate our study’s results.

RESULTS
Baseline characteristics
All 50 patients underwent SRT; however, one patient was excluded from the intention-to-treat (ITT) group due to failure to attend at least one follow-up visit. Finally, 52 eyes of 49 patients were included in the ITT group for efficacy analysis. Detailed demographic information of the ITT group is shown in online supplemental table 1. The mean age of the patients was 50.7±8.6 years. Regarding CSC characteristic, 44 patients presented chronic disease (89.8%, 47 eyes) and 5 acute (10.2%, 5 eyes), with symptom durations ranging from 1 to 217 (mean±SD: 44.24±48.5) months.

Primary outcomes
For the primary analysis, the means of BCVA, CRT and peak SRF height at baseline and 1, 3 and 6 months after treatment were measured, as presented in table 1. The mean BCVA of 52 eyes was improved from 0.15±0.18 logMAR at baseline to 0.14±0.18, 0.11±0.17 and 0.12±0.21 logMAR at 1, 3 and 6 months, respectively. BCVA improved significantly at 3 months (p=0.017), but only slightly at 6 months (p=0.062; online supplemental figure 2A). Detailed changes in BCVA from baseline to 6 months in each eye are presented in online supplemental figure 2B.

Compared with the BCVA, a clearly significant improvement in the mean CRT was observed 1 month after SRT. The mean CRT improved from 350.6±100.1 µm to...
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at baseline to 276.6±78.2 µm at 1 month (p<0.001), 269.6±65.9 µm (p<0.001) at 3 months and 268.2±70.6 µm at 6 months (p<0.001; online supplemental figure 2C). A scatter plot showed that CRT improved from baseline to 6 months in most of the treated eyes (online supplemental figure 2D).

Similar to the changes in CRT, the mean peak SRF height improved significantly from 152.1±86.1 µm at baseline to 81.9±80.8 µm at 1 month (p<0.001), 67.5±67.7 µm at 3 months (p<0.001) and 63.4±76.3 µm at 6 months (p<0.001; online supplemental figure 2E). The cumulative complete SRF resolution rate gradually increased from 1 month to 6 months after SRT (online supplemental figure 2F). Complete SRF resolution was observed in 62% of eyes (32 eyes) at 6 months. Figure 1 presents high-resolution OCT images of a representative case. The patient presented a 30-month history of CSC symptoms and 191 µm peak SRF height at baseline. The SRF height decreased continuously during the follow-up period and resolved completely 6 months after treatment.

Long-term outcomes

To examine the long-term treatment effects, BCVA and CRT were analysed for patients that were available for follow-up visits for up to 24 months (table 2). BCVA improvement was significant after 9 months until the last visit, but not at 6 months (online supplemental figure 3A). The mean BCVA of the last visit was 0.09±0.21, significantly different from the 0.15±0.18 baseline mean BCVA (p=0.012). Regarding CRT, a continuous and significant reduction was observed from the primary assessment at 6 months to the last visit (online supplemental figure 3B). The mean CRT reduced from 350±100 µm at baseline to 259±70 µm at the last visit (p<0.001). The SRF resolutions were achieved in 35 eyes.
Furthermore, in the SR T-T trial, 17 20 22 confirming the effectiveness of SRT in reducing the CRT and SRF height of eyes affected by CSC. Notably, 90% of the patients in this study had chronic CSC with persistent SRF. We observed early improvement in CRT within 1 month, highlighting the beneficial effects of SRT in this study. The early improvement of CRT in the current study is consistent with the findings of a randomised controlled trial that demonstrated that SRT leads to faster resolution of SRF compared with sham treatment.18

Although significant BCVA improvement in SRT for CSC has been reported in several studies,17 20 21 one study developed herpes zoster. Nevertheless, none of these events were considered to be associated with SRT. Thus, no SRT-related adverse events were reported during the follow-up period.

**DISCUSSION**

In this 24-month follow-up real-world prospective study, we evaluated the safety and efficacy of SRT using a Q-switched Nd:YLF laser with an RTF system in patients with CSC. We observed a significant improvement in CRT and SRF height, with complete SRF resolution in 62% and 67% of the treated eyes 6 months after treatment and at the last visit, respectively. In addition, a correlation between the reduction in SRF height and improvement in BCVA was identified, and the concomitant treatment effect was analysed.

We observed that SRF resolved completely in 62% of the patients at 6 months after treatment. The complete SRF resolution rate at 6 months in previous studies on SRT ranged from 50% to 90%.19–21 Notably, one study that achieved a 90.5% SRF resolution rate at 6 months allowed retreatment 3 months after the initial therapy.21 A favourable outcome from retreatment at 3 months was also demonstrated by another study.22 Moreover, the SRF resolution rate at 7–8 months was 67.2% and 28.8% for PDT-treated and high-density SMPL-treated patients, respectively, in the PLACE trial.23 Hence, our results showed an SRF resolution rate comparable to that of previous studies on SRT and PDT treatment.

In the current study, both CRT and SRF heights significantly reduced at 1 month to the end of the follow-up period. Such findings are consistent with those of previous studies on SRT for CSC,17 20 22 confirming the effectiveness of SRT in reducing the CRT and SRF height of eyes affected by CSC. Notably, 90% of the patients in this study had chronic CSC with persistent SRF. We observed early improvement in CRT within 1 month, highlighting the beneficial effects of SRT in this study. The early improvement of CRT in the current study is consistent with the findings of a randomised controlled trial that demonstrated that SRT leads to faster resolution of SRF compared with sham treatment.18

**Table 3 Concomitant treatment and SRT-only subgroup analysis outcomes**

<table>
<thead>
<tr>
<th></th>
<th>BCVA (mean±SD; logMAR)</th>
<th></th>
<th>CRT (mean±SD; µm)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Last visit</td>
<td>P value*</td>
<td>Baseline</td>
</tr>
<tr>
<td>Concomitant treatment group</td>
<td>0.24±0.2</td>
<td>0.19±0.28</td>
<td>0.3</td>
<td>347±85</td>
</tr>
<tr>
<td>SRT-only group</td>
<td>0.12±0.16</td>
<td>0.07±0.2</td>
<td>0.03</td>
<td>355±105</td>
</tr>
<tr>
<td>P value†</td>
<td>0.04</td>
<td>0.1</td>
<td></td>
<td>0.5</td>
</tr>
</tbody>
</table>

*P value for difference test between last visit and baseline.
†P value for difference test between two subgroups.

**Post hoc analysis**

Linear regression analysis was performed to examine the correlation between symptom duration and treatment outcomes, including changes in BCVA, CRT, peak SRF height, SRF resolution rate and the time to achieve complete SRF resolution. No significant association was observed between symptom duration and treatment outcomes. However, a significant correlation was observed between the reduction in peak SRF height and BCVA improvement at 6 months ($r=−0.357$, $p=0.009$).

Figure 3A demonstrates a linear regression line.

**Effect of concomitant treatment**

In this study, the use of concomitant treatments, including anti-VEGF intravitreal injections and PDT, was permitted by the principal investigator. During the study period, 14 (27%) eyes received concomitant treatment, as follows: 2 received PDT, 10 received anti-VEGF intravitreal injection and 2 received both PDT and anti-VEGF treatment. A post hoc analysis was conducted to compare the subgroup that received concomitant treatment ($n=14$) and the subgroup that received only SRT ($n=38$; table 3).

The analysis showed that the baseline BCVA, yet not the baseline CRT, was significantly lower in the concomitant treatment group compared with the SRT-only group. Furthermore, in the SRT-only group, BCVA at the last visit was significantly improved compared with that at baseline. In the concomitant treatment group, BCVA improved, although not significantly (online supplemental figure 4A). CRT was significantly reduced in both groups at the final visit (online supplemental figure 4B). However, no significant difference was observed between the two subgroups in terms of changes in BCVA and CRT from baseline to the last visit.

**Adverse events**

Three adverse events were reported in two patients: one experienced pain exacerbation due to thoracic myelopathy and a car accident, while the other patient increasing the SRF resolution rate to 67% at the last visit compared with 62% at 6 months (online supplemental figure 3C).

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reported a non-significant improvement.\textsuperscript{22} In this study, although CRT was remarkably reduced from 1 month after treatment, BCVA improvement was delayed, suggesting a delay in functional improvement compared with structural improvement. This can be explained by a previous study that described three phases of retinal reactions to SRT,\textsuperscript{24} which suggested that functional recovery was initiated after SRF resorption. Furthermore, the baseline visual acuity in this study was relatively good, which could have undermined the BCVA improvement at 6 months. While a study with similar good baseline BCVA value showed insignificant vision improvement, another study with worse baseline BCVA value of 0.41 logMAR showed significant improvements of vision to 0.33 logMAR.\textsuperscript{21, 22}

Regarding the long-term effects of SRT, improvements in CRT and BCVA were observed for up to 24 months after treatment. To our knowledge, no prospective studies on CSC treatment using SRT with a follow-up period of up to 24 months had yet been conducted. Moreover, because CSC is usually a recurrent and chronic disease requiring multiple treatments, a longstanding treatment effect could potentially reduce the burden of retreatment. No SRT-related adverse events were observed during the long-term follow-up, confirming the safety of the treatment. This is consistent with a previous study of 1.7 µs pulse laser SRT that demonstrated that no scotoma or reduction in retinal sensitivity was associated with SRT spots.\textsuperscript{14}

In the post hoc analysis, no correlations between symptom duration and visual outcomes were observed. These findings are consistent with that of a previous study showing that symptom duration was not correlated with the rate of change in central macular thickness or complete SRT resolution.\textsuperscript{20} In contrast, we discovered a significant correlation between BCVA improvement and a reduction in SRF height. We hypothesised that patients with a higher SRF height would have a greater likelihood of experiencing reduced visual acuity, resulting in a more significant improvement in BCVA with a larger reduction in SRF height. This is supported by a previous study on SRT for clinically significant diabetic macular oedema, which showed a correlation between BCVA improvement and CRT.\textsuperscript{25} The correlation between SRF height change and BCVA improvement highlights the importance of structural restoration, which contributes to functional visual improvement.

In this study, concomitant treatments, including PDT and anti-VEGF injections, were used as rescue treatments in 27% of the studied eyes. Both the subgroup that received solely SRT and the one that received SRT with concomitant treatments showed significant improvements in retinal structure. No significant difference was observed in treatment efficacy between the two subgroups, indicating that concomitant treatment could be avoided in 73% of the studied eyes. This finding reflects real-world clinical practice outcomes and suggests that SRT could be considered an initial treatment option to lessen the need for concomitant treatments.

Several hypotheses have been proposed for the treatment mechanism of SRT in CSC. In the PLACE trial, PDT was superior to SMPL for CSC treatment.\textsuperscript{23} Although SRT employs a microsecond-pulse laser, its therapeutic mechanism differs from that of SMPL. While SMPL does not cause RPE damage, SRT selectively damages RPE cells.\textsuperscript{26} Despite choroidal hyperpermeability being considered the primary factor in the pathophysiology of CSC, RPE dysfunction has been suggested to play a role in CSC development,\textsuperscript{27} suggesting that SRT may ameliorate CSC by restoring RPE cell functions. Furthermore, previous studies have shown that SRT may increase the secretion of active matrix metalloproteinases and decrease VEGF,\textsuperscript{28, 29} proposing an additional therapeutic mechanism of SRT in CSC.

The limitation of this study is that such was an extended observational investigation of a prospective study. Half of the enrolled patients were followed up for 24 months. Thus, the long-term treatment efficacy could have been underestimated if patients with favourable outcomes were missing, or vice versa.

In conclusion, SRT using a 527 nm, 1.7 µs Nd:YLF laser with RTF technology was safe and lead to anatomical improvement in a treatment regimen that simulated real-world clinical practice settings. Additionally, the treatment effects persisted for up to 24 months after SRT. These findings suggest that SRT should be considered as a treatment modality for patients with CSC in real-world practice.

Contributors CKY conducted the investigation process, specifically performing the treatments, data collection, data analysis and manuscript writing. HGY supervised the study, reviewed and revised the manuscript and was responsible for the study planning and execution. HGY is the guarantor of this work.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants. This study was performed at the Seoul National University Hospital, Republic of Korea, and the study protocol was approved by the Institutional Review Board (D-1702-144-834). This study was conducted in accordance with the tenets of the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets generated and analysed in the current study are available from the corresponding author upon reasonable request.

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