EFFECT OF ORAL CARBONIC ANHYDRASE INHIBITOR ON CYSTOID MACULAR EDEMA ASSOCIATED WITH RETINITIS PIGMENTOSA

An OCT and OCT Angiography Study

JOON HYUNG YEO, MD,* CHAN HONG MIN, MD,† YOUNG HEE YOON, MD, PhD†

Purpose: To investigate the factors associated with visual improvement in response to oral carbonic anhydrase inhibitors (CAIs) and the occurrence of microvascular changes in patients with retinitis pigmentosa–associated cystoid macular edema (RP-CME).

Methods: This retrospective cohort study included 59 eyes from 39 patients with RP-CME who underwent at least 3 months of oral CAI treatment. The eyes were divided into responding and nonresponding groups based on optical coherence tomography (OCT) criteria (resolution of cyst and reduction of foveal or parafoveal volume). All eyes were assessed before and after treatment using OCT and OCT angiography.

Results: Thirty-three eyes (55.9%) demonstrated a positive response to treatment, and 26 eyes (44.1%) did not. Compared with nonresponding eyes, responding eyes had a significantly higher frequency of multilayer CME than CME limited to the inner nuclear layer ($P = 0.016$). Subgroup analysis within the responding group revealed that improvements in visual acuity were more likely in eyes with fovea-involving CME and a higher baseline external limiting membrane and ellipsoid zone width. Microvascular parameters showed no significant changes after treatment.

Conclusion: Eyes with CME extending to the outer nuclear layer or central fovea, and higher initial photoreceptor integrity may be prognostic factors associated with structural and functional improvements after carbonic anhydrase inhibitors treatment. Early treatment of multilayer CME with foveal involvement seems to be crucial in preventing irreversible photoreceptor damage.

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Retinitis pigmentosa (RP) causes night blindness and progressive peripheral visual field loss, with gradual deterioration of central visual acuity. The development of ocular complications, including cystoid macular edema (CME), can further reduce visual acuity at any stage of the disease. The prevalence of RP-associated CME (RP-CME), as detected by optical coherence tomography (OCT), ranges between 5.5% and 49%.1–4

RP-CME treatment may improve vision even if the underlying disorder continues to progress. Several therapeutic options, including laser therapy, topical and oral carbonic anhydrase inhibitors (CAIs), periocular and intravitreal steroids, intravitreal antivascular endothelial growth factor (anti-VEGF) agents, and even vitrectomy have been reported.5 Although positive effects are not consistently observed in all patients, topical or oral CAIs are frequently used as an initial therapeutic approach.

In our previous report using OCT angiography (OCTA), we found no reduction in vascular density or focal vascular disruption of retinal capillary plexuses in patients with RP-CME.6 To date, no studies have...
investigated microvascular changes elicited by CAI treatment in patients with RP.

This study aimed to investigate the factors associated with the response of patients with RP-CME to oral CAI and improvement in their visual function and to explore whether microvascular changes occurred after treatment.

**Methods**

All procedures conformed to the tenets of the Declaration of Helsinki, and the study design was approved by the Institutional Review Board of Asan Medical Center (Seoul, Korea; IRB No. 2020-0291). The need for written informed consent was waived due to the retrospective nature of this study.

**Patients**

This retrospective cohort study identified all patients treated at Asan Medical Center between March 2017 and May 2021 with the term “retinitis pigmentosa” appearing in their electronic records. Data collected from records included age, sex, best-corrected visual acuity (BCVA), and OCT and OCTA findings. The BCVA in Snellen values was converted to the logarithm of the minimum angle of resolution for statistical analysis.

Patients were included in this study if they met the following inclusion criteria: (1) confirmed diagnosis of unilateral or bilateral RP-CME (if bilateral, each eye was evaluated individually); (2) treatment with oral CAI; and (3) pretreatment OCT/OCTA scans acquired within 2 weeks of treatment initiation and posttreatment OCT/OCTA scans acquired at least 3 months after treatment initiation.

Patients were excluded if any of the following criteria were met: (1) other treatments for RP-CME within 3 months of initiation of oral CAI; (2) history of vitrectomy or concomitant ocular diseases other than cataracts; (3) low-quality OCT and OCTA images because of media opacity or poor fixation; (4) refractive errors (spherical equivalent) of -6 diopters or greater; or (5) history of systemic diseases with an established effect on retinal vasculature.

**Optical Coherence Tomography and Optical Coherence Tomography Angiography Imaging**

An Optovue RTVue XR Avanti with AngioVue imaging system (Optovue, Fremont, CA) was used to obtain the OCT and OCTA images. We selected the 6-mm retinal map analysis protocol, with 250-μm intervals in the central 4-mm area, for the volume scans to reconstruct a surface map with numeric averages of the measurements for each of the nine map sectors, as previously defined by the Early Treatment Diabetic Retinopathy Study (ETDRS).

First, RP-CME was classified by the vertical and horizontal distributions of the CME as previously reported. For the vertical distribution, eyes were divided into inner nuclear layer (INL)-only CME or multilayer CME (INL + outer nuclear layer [ONL] ± ganglion cell layer [GCL]). For the horizontal distribution, eyes were divided into parafovea-only CME (pCME) or parafoveal and foveal CME (fiCME) according to central fovea involvement (central 1-mm circle).

In addition, OCT parameters included central foveal thickness (CFT), parafoveal thickness, central foveal volume, parafoveal volume, horizontal width of the residual external limiting membrane (ELM) and ellipsoid zone (EZ) line, and subfoveal choroidal thickness (SFCT). A horizontal scan through the fovea was used to evaluate the horizontal width of the residual ELM and EZ lines and the SFCT using the measuring tool. Termination of the EZ was determined using a previously described protocol. The SFCT was the average of the choroidal thickness, which was measured manually by two independent investigators (J.H.Y. and C.H.M.) at seven locations (subfoveal region and at 1000-μm intervals from the fovea to 3,000 μm in the nasal and temporal positions). Each investigator obtained five measurements per image and discarded the maximal and minimal values. The mean value of the remaining measurements was used in subsequent analyses.

To acquire the OCTA images, macular 3 × 3 mm² scans were performed. All images were assessed independently by two investigators (J.H.Y. and C.H.M.) to ensure correct segmentation and sufficient quality of the images. In cases of incorrect segmentation, the boundary was manually adjusted using the AngioVue module. Images with insufficient quality were excluded according to the following criteria: (1) images not centered on the macula; (2) presence of focus loss, blink lines, motion artifacts, specular dots, or edge duplication; and (3) images with segmentation errors because of extensive retinal degeneration. The parameters registered included foveal and parafoveal flow densities (FDs) of the superficial capillary plexus (SCP), deep capillary plexus (DCP), choriocapillaris, and foveal avascular zone (FAZ).

**Oral Carbonic Anhydrase Inhibitors Treatment**

Oral CAI therapy (125–500 mg/day) was initiated in all patients. The treatment dose was chosen based on...
the discretion of the treating physician. Follow-up visits were scheduled for 1 month to 3 months after treatment initiation, and the follow-up interval was based on various factors. At each visit, OCT and OCTA scans were performed to determine the improvement in CME. If the patient failed to demonstrate a significant response but the treatment was well-tolerated, the dosage was maintained. If oral CAI was not well-tolerated or if improvement was observed, the dosage was gradually tapered.

A positive treatment response was considered to be achieved when the eyes met the following criteria: one or more complete resolutions of cyst and a decrease of at least 4% in foveal volume or in parafoveal volume in at least one of the four parafoveal ETDRS quadrants. To assess the complete resolution of the cyst, two independent investigators (J.H.Y. and C.H.M.) blinded to the volumetric macular scans and other clinical data independently reviewed the pretreatment and posttreatment structural OCT raster scans. In cases of disagreement, a third blinded investigator (Y.H.Y.) adjudicated the decision.

Statistical Analysis

All statistical analyses were performed using the SPSS software (v. 26.0; IBM Corp, Armonk, NY). Continuous variables are presented as mean ± SD. Intergroup comparisons for continuous variables were evaluated using a paired t-test, a Mann–Whitney U test, or a Wilcoxon signed-rank test, as appropriate. The chi-square test or the Fisher exact test was used to compare categorical variables. Statistical significance was set at P < 0.05.

Results

After application of the inclusion and exclusion criteria, 59 eyes from 39 patients were included in this study. Twenty of these patients had bilateral RP-CME, whereas the remaining 19 had unilateral RP-CME. The mean age of the patients was 44.7 ± 17.3 years (range: 22–82 years). The characteristics of the eyes included in this study are summarized in Table 1.

Baseline Characteristics

Of the 59 eyes included in this study that received oral CAI, 33 eyes (55.9%) demonstrated a positive response to treatment, whereas the remaining 26 (44.1%) did not respond. No patient showed asymmetrical response to oral CAI in either eye. The baseline clinical characteristics of the two groups are summarized in Table 2. Compared with patients with nonresponding eyes, patients with responding eyes were significantly older (49.3 ± 17.1 vs. 38.9 ± 16.0, P = 0.024) and had significantly worse BCVA (0.35 ± 0.27 [Snellen equivalent, 20/45] vs. 0.19 ± 0.17 [Snellen equivalent, 20/31], P = 0.009). In addition, responding eyes had a significantly higher frequency of multilayer CMEs (P = 0.016). There were no significant differences in macular thickness, macular volume, SFCT, or ELM/EZ width. Longer treatment duration and higher cumulative doses of oral CAI were observed in nonresponding eyes than in responding eyes, but these differences were not statistically significant (7.00 ± 5.76 vs. 8.27 ± 5.95, P = 0.345; and 37.50 ± 25.83 vs. 45.18 ± 42.46, P = 0.560; Table 2).

Changes in Optical Coherence Tomography and Optical Coherence Tomography Angiography Parameters

After oral CAI treatment, responding eyes showed a statistically significant decrease in anatomical parameters concerning thickness and volume, whereas nonresponding eyes did not (Table 3, Figures 1 and 2). However, SFCT was significantly decreased in both responding and nonresponding eyes (258.48 ± 106.32 vs. 252.21 ± 106.31, P = 0.014 and 257.00 ± 111.13 vs. 244.42 ± 109.03, P = 0.010, respectively). Table 4 summarizes the microvascular characteristics of the responding and nonresponding eyes before and after treatment. The foveal and parafoveal FD at the SCP, DCP, and FAZ showed no statistically significant changes before and after treatment. Although both groups seemed to have decreased FD on OCTA, no improvement in focal vascular disruption or capillary dropout, especially in areas of CME, was detected (Figures 1 and 2).

Best-Corrected Visual Acuity Changes and Predictors of Best-Corrected Visual Acuity Improvement

The mean BCVA improved from 0.35 ± 0.27 (Snellen equivalent, 20/45) to 0.31 ± 0.29 (Snellen equivalent, 20/41; P = 0.047) in responding eyes. The BCVA improved in 12 of 33 responding eyes (36.4%) and deteriorated only in one responding eye (3.0%). The remaining 20 of 33 responding eyes (60.6%) demonstrated no change in their BCVA. In nonresponding eyes, BCVA tended to get worse from 0.19 ± 0.17 (Snellen equivalent, 20/31) to 0.22 ± 0.15 (Snellen equivalent, 20/33), although this difference was not statistically significant (P = 0.051). Interestingly, responding eyes, BCVA improvement
was observed in 11 of 22 eyes with fCME, while only 1 of 11 eyes without foveal involvement (pCME) showed BCVA improvement \((P = 0.027, \text{Table 5})\). In addition, eyes with multilayer CME tended to show visual improvement, but these differences were not statistically significant \((P = 0.054; \text{Table 5})\). Eyes that showed BCVA improvement had a higher ELM and EZ width than eyes that did not show BCVA improvement \((P = 0.005 \text{ and } P = 0.011; \text{Table 5})\). No baseline OCTA parameters showed any significant differences according to visual improvement (data not shown).

### Discussion

CME is one of the few treatable causes of vision loss in RP. In this retrospective study of 59 eyes treated with oral CAI, we compared pretreatment and posttreatment OCT and OCTA images. After treatment, there was resolution of the cyst and a significant volume reduction in 33 eyes and visual improvement in 12 eyes. It was found that 23 out of 33 eyes affected by multilayer CME showed a response (69.7%). By contrast, only 10 of 26 eyes affected by INL-only CME responded to treatment (38.5%). Among responding eyes, those with fCME and higher baseline ELM and EZ widths were more likely to show BCVA improvement. In addition, we confirmed that eyes with RP-CME did not show a significant change in FD within individual capillary layers after oral CAI treatment.

In previous studies, patients with RP were considered to have responded to treatment if they achieved a CFT reduction of 11.0% or above.8–11 However, based on our previous finding that RP-CME is mostly located in the INL of the parafoveal macula, we considered that treatment response for CFT reduction may underestimate the improvement of pCME. In fact, pCME accounted for 55.9% of the eyes in this study. In addition, CFT can vary substantially among individuals owing to factors such as age, sex, refractive error, and even the degree of degenerative change in RP. With the advent of OCT technology, volumetric macular scans for OCTA can be acquired within a few seconds. You et al assessed the sensitivity and specificity of CFT and central macular fluid volume (CMFV) using macular OCTA volumetric scans for the diagnosis of diabetic macular edema (DME) and suggested that measurement of CMFV may improve diagnostic accuracy for DME as well.12 Therefore, we hypothesized that changes in foveal and parafoveal volume could be more useful for assessing the response to oral CAI in RP-CME. In this study, a treatment response to oral CAI was observed in 55.9% of the eyes included, a percentage which is somewhat higher than that reported in a previous study that used CFT-based OCT criteria to define treatment response.13 A possible reason for the higher response rate in our study included the use of macular volume-

### Table 1. Baseline Clinical Characteristics of the Eyes Included in This Study

|        | RP-CME Eyes \((n = 59)\) |        |        |
|--------|--------------------------|--------|--------|
| Mean age, years | 44.7 (17.3) | Range, years | 22–82 |
| Female, n (%) | 38 (64.4) | BCVA, logMAR | 0.28 (0.24) |
| ELM width, \(\mu m\) | 3,375.44 (2011.01) | Total volume, \(\mu m^3\) | 2.11 (0.23) |
| INL-only CME: Multilayer CME, n | 26 (44.1) | INL-only CME: Multilayer CME, n | 26 (44.1) |
| pCME: fCME, n (%) | 33 (55.9) | Duration of oral CAI use, months | 7.56 (5.78) |

*Data are presented as mean (SD), unless otherwise indicated.*

### Table 2. Comparisons in Baseline Characteristics Between Responding and Nonresponding Eyes

|                      | Responding Eyes \((n = 33)\) | Nonresponding Eyes \((n = 26)\) | \(P\) |
|----------------------|-------------------------------|-------------------------------|------|
| Mean age, years      | 49.3 (17.1)                  | 38.9 (16.0)                  | 0.024*|
| BCVA, logMAR         | 0.35 (0.27)                  | 0.19 (0.17)                  | 0.009*|
| INL-only CME: Multilayer CME, n | 10:23 | 16:10 | 0.016† |
| pCME: fCME, n (%)    | 33 (55.9) | 26 (44.1) | 0.345* |
| Duration of oral CAI use, months | 7.00 (5.76) | 8.27 (5.95) | 0.560* |
| Cumulative dose of oral CAI, g | 37.50 (25.83) | 45.18 (42.46) |      |

*Data are presented as mean (SD), unless otherwise indicated.*

*Statistical comparison using the Mann–Whitney U test.
†Statistical comparison using the chi-square test.*
Table 3. Comparisons of Pretreatment and Posttreatment Optical Coherence Tomography Parameters in Responding Eyes and Nonresponding Eyes

| Parameter             | Responding Eyes (n = 33) | Nonresponding Eyes (n = 26) | P* | P† |
|-----------------------|--------------------------|-----------------------------|----|----|
| CFT, μm              | 267.79 (51.20)           | 240.12 (39.60)              | <0.001 | 276.38 (57.45) | 282.00 (65.84) | 0.306 |
| PFT, μm              | 297.76 (37.75)           | 286.76 (34.30)              | <0.001 | 306.62 (24.70) | 307.77 (30.23) | 0.686 |
| SFCT, μm             | 258.48 (106.32)          | 252.21 (106.31)             | 0.014 | 257.00 (111.13) | 244.42 (109.03) | 0.010 |
| Foveal volume, μm³   | 0.21 (0.04)              | 0.19 (0.03)                 | <0.001 | 0.22 (0.05) | 0.22 (0.05) | 0.176 |
| Parafoveal volume, μm³ | 1.87 (0.24)            | 1.80 (0.22)                 | <0.001 | 1.93 (0.15) | 1.93 (0.19) | 0.638 |
| Total volume, μm³    | 2.08 (0.26)              | 1.99 (0.24)                 | <0.001 | 2.14 (0.19) | 2.16 (0.23) | 0.780 |
| ELM width, μm        | 3,123.06 (2028.83)       | 3,069.76 (2019.68)          | 0.276 | 3,695.77 (2201.06) | 3,667.81 (2049.22) | 0.324 |
| EZ width, μm         | 2,521.67 (2058.32)       | 2,457.12 (2037.70)          | 0.179 | 3,018.69 (2215.73) | 3,042.62 (2233.70) | 0.849 |

Data are presented as the mean (SD).
*Statistical comparison between pretreatment and posttreatment data of responding eyes using the paired t-test.
†Statistical comparison between pretreatment and posttreatment data of nonresponding eyes using the Wilcoxon signed-rank test.

Based OCT criteria, which reflected pCME improvement with more sensitivity.

Although several mechanisms have been proposed to explain the etiology of RP-CME, we previously found no alteration of microvascular parameters. This suggests that RP-CME may not be primarily vasculogenic but may be related to Müller cell dysfunction. In addition, we showed that most cysts in eyes affected by RP-CME were located in the INL and within the parafoveal macula. When CME extended to the ONL, it tended to involve the central macula and damage foveal photoreceptors. Based on our previous findings on the spatial distribution of RP-CME, we hypothesized that RP-CME progressed from INL to ONL or GCL (multilayer CME), or from pCME to fCME, and that this progression led to the disruption of foveal photoreceptors and subsequent visual deterioration.

In this study, responding eyes had a significantly higher frequency of multilayer CME. In addition, compared with pCME, fCME seemed to be more responsive to oral CAI treatment. According to our hypothesis for RP-CME progression, CAI treatment becomes more effective when RP-CME progresses to the ONL or central fovea than when RP-CME is limited to the INL and within the parafoveal macula. Therefore, aggressive treatment should be considered when CME involves the central macula and progresses to the ONL. We also found that higher initial ELM and EZ widths predicted a favorable response to oral CAI. Considering that ONL fluid may damage the underlying photoreceptors, resulting in EZ disruption, early treatment of multilayer CME with foveal involvement seems to be a good strategy in preventing irreversible photoreceptor damage.

The OCTA results confirmed that there were no significant changes in FD after oral CAI treatment in both responding and nonresponding eyes. In the context of DME or retinal vein occlusion (RVO), an improvement in FD after anti-VEGF injections was positively correlated with visual acuity. The lack of significant changes in FD after CME treatment observed in this study suggests that RP-CME may not be primarily vasculogenic.

Unlike the case for vasculogenic CME such as DME and RVO, we have quite frequently observed mild or no fluorescein leakage in RP-CME eyes, which has been described in many previous studies. Further impairment of the barrier function is impaired under pathologic conditions by the secretion of VEGF and tumor necrosis factor, which increases vascular permeability. In addition, the expression of pigment epithelium-derived factor is reduced under pathologic conditions in the retina and in Muller cells, resulting in an upregulation of VEGF in Muller cells and further impairment of the barrier function. Thus, we presume that the mild degree of fluorescein leakage observed in RP-CME may be caused by breakdown of the capillary barrier induced by Muller cells.

The rationale for the use of oral or topical CAIs involves increasing retinal pigment epithelium (RPE) pumping. Several studies have demonstrated the efficacy of oral and topical CAIs in RP-CME, and a response to treatment with these therapeutic agents has been reported in up to 60% of patients. In this study, despite differences in the criteria used to define a positive response, we observed that 55.9% of eyes showed an improvement after treatment. In agreement with findings from a previous study, eyes with CME that extended to the ONL were more likely to respond to treatment. It has been postulated that CAI might reduce...
ONL fluid more effectively than INL fluid due to better access to the RPE basolateral membrane than to the neurosensory retina. However, in this study, 10 of 33 eyes with ONL fluid did not respond to oral CAI, suggesting that the treatment effect may not be simply derived from enhanced RPE pumping activity. Because Müller cells are known to have large amounts of active carbonic anhydrase, inhibition of this enzyme in Müller cells may play a relevant role in the observed effects.

Despite the effectiveness of oral CAI at the anatomical level, reports on its functional efficacy have been inconsistent. In this study, among 33 responding eyes, 12 eyes showed an improvement in BCVA, while the remaining 21 failed to show improvements despite comparable decreases in macular thickness and volume. Eyes with BCVA improvement had larger ELM and EZ widths at baseline. Interestingly, most eyes with BCVA improvement showed CME extending to the ONL (91.7%) or involving the central fovea (91.7%). We hypothesize that these eyes affected by multilayer CME responded well to CAI and exhibited subsequent functional improvement when they were treated before photoreceptor degeneration. By contrast, if the eye had longstanding CME resulting in EZ disruption, BCVA did not respond to CAI treatment, even if improvement at the anatomical level was evident. We conclude that timely CME treatment is critical for preserving residual vision in patients with RP-CME.

This study has several limitations. First, because of its retrospective nature, the follow-up period and treatment duration varied. Second, as genetic characterization of RP was not generally available, this information was not included in this study. Future studies are needed to evaluate whether different genetic backgrounds may influence the response to oral CAI. Third, this study included a relatively small number of patients. Further large-scale prospective studies with longer follow-up periods are needed to clarify whether anatomical improvement leads to functional improvement and to investigate whether persistent CME is associated with long-term vision.

Fig. 1. Representative OCT and OCTA images of eyes with retinitis pigmentosa–associated cystoid macular edema (RP-CME) responded to oral CAI. A. Pretreatment and posttreatment OCT and OCTA images of an eye with parafoveal CME. B. Pretreatment and posttreatment OCT and OCTA images of an eye with CME involving the fovea. Regardless of treatment response, RP-CME eyes did not show a significant change in vascular density or improvement in focal vascular disruption, especially in the CME areas, after treatment. VA, visual acuity; FV, foveal volume; PV, parafoveal volume.
loss. Finally, we excluded eyes with epiretinal membranes and vitreomacular traction, but we cannot exclude the possibility that vitreomacular interface disease may be associated with the development of RP-CME.

In conclusion, we demonstrated that 55.9% of eyes with RP-CME showed improvements at the anatomical level after oral CAI treatment. BCVA improved when photoreceptor integrity was preserved at baseline. Eyes with CME extending to the ONL or central fovea were more likely to respond to CAI treatment and show subsequent visual improvement. Macular vascular density was not significantly altered by CAI treatment. Based on these observations, we recommend early treatment of multilayer CME with foveal involvement to

Table 4. Comparisons of Pretreatment and Posttreatment Optical Coherence Tomography Angiography Parameters in Responding and Nonresponding Eyes

|                      | Responding Eyes (n = 33) |          | Nonresponding Eyes (n = 26) |          |
|----------------------|--------------------------|----------|-----------------------------|----------|
|                      | Pretreatment              | Posttreatment |  | Pretreatment              | Posttreatment |  |
| SCP foveal FD        | 18.78 (4.93)             | 18.02 (4.46) | 0.057 | 22.12 (6.01)             | 22.73 (5.28) | 0.089 |
| Parafoveal FD        | 44.52 (4.18)             | 44.00 (5.04) | 0.190 | 47.20 (3.03)             | 46.89 (3.34) | 0.632 |
| DCP foveal FD        | 28.98 (6.41)             | 29.71 (7.26) | 0.364 | 34.53 (6.40)             | 34.01 (6.77) | 0.294 |
| Parafoveal FD        | 41.02 (6.98)             | 41.75 (7.61) | 0.328 | 42.19 (5.77)             | 40.83 (5.97) | 0.204 |
| Choriocapillaris foveal FD | 51.92 (7.16) | 53.17 (7.47) | 0.086 | 54.91 (7.86)             | 53.20 (6.82) | 0.278 |
| Parafoveal FD        | 60.87 (5.90)             | 62.23 (6.26) | 0.216 | 59.51 (5.45)             | 59.33 (5.96) | 0.861 |
| FAZ, mm²             | 0.31 (0.11)              | 0.31 (0.11) | 0.111 | 0.25 (0.07)              | 0.25 (0.07)  | 0.661 |

Data are presented as mean (SD).
*Statistical comparison using the paired t-test.
prevent irreversible structural damage and to potentially decelerate underlying photoreceptor loss.

**Key words:** retinitis pigmentosa, cystoid macular edema, optical coherence tomography angiography, carbonic anhydrase inhibitor.

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