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DEXAMETHASONE IMPLANT VERSUS TOPICAL CARBONIC ANHYDRASE INHIBITORS IN PATIENTS WITH BILATERAL RETINITIS PIGMENTOSA–RELATED CYSTOID MACULAR EDEMA

A Prospective, Paired-Eye Pilot Study

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Purpose: To compare within-subject efficacy and safety of intravitreal dexamethasone implant and topical carbonic anhydrase inhibitors in the treatment of retinitis pigmentosa–related cystoid macular edema.

Methods: Patients with bilateral retinitis pigmentosa–related cystoid macular edema were treated with intravitreal dexamethasone implant in one eye and topical carbonic anhydrase inhibitors in the contralateral eye. The primary endpoint was a change in central macular thickness. Secondary endpoints were changes in best-corrected visual acuity and microperimetric central retinal sensitivity. Intraocular pressure and other ocular complications were evaluated for safety assessment.

Results: Nine patients were recruited for this 12-month follow-up study. Central macular thickness was significantly lower in intravitreal dexamethasone implant–treated eyes than in topical carbonic anhydrase inhibitors–treated eyes at Months 1 and 7, whereas mean best-corrected visual acuity was better in eyes treated with topical carbonic anhydrase inhibitors at Month 12 (borderline significant $P = 0.0510$). There was no difference in microperimetric sensitivity between the two treatments. Three patients developed ocular hypertension after intravitreal dexamethasone implant. Intravitreal dexamethasone implant showed an effect on the contralateral eye in five of nine patients.

Conclusion: Intravitreal dexamethasone implant was more effective than topical carbonic anhydrase inhibitors in reducing retinitis pigmentosa–related cystoid macular edema 1 month after treatment. Corticosteroids can play a key role in the management of retinitis pigmentosa–related cystoid macular edema; however, their routes, timing, and modes of administration should be further explored.

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Retinitis pigmentosa (RP) is a group of inherited retinal dystrophies that lead to a gradual loss of vision and eventually blindness; it affects approximately 1 in 4,000 persons worldwide. These dystrophies involve a progressive loss of rods and subsequently cones, resulting in early nyctalopia and loss of peripheral vision.[1] Although central vision is typically spared until advanced stages of the disease, cystoid macular edema (CME) is a common compli-

cation, with a reported prevalence of up to 49%.[2,3] If left untreated, CME can cause significant visual impairment, which is why early detection and management are crucial for preserving visual function in patients with RP.

The exact etiopathogenesis of RP-related CME is not yet clear, but possible mechanisms include increased vascular permeability, failure of retinal pigment epithelium pumping activity, an autoimmune

process (antiretinal antibodies), and Müller cell dysfunction. Inflammation is also believed to play an important role in the development of RP-related CME.[4]

Our limited understanding of the pathogenesis of RP-related CME poses a challenge for patient management and creates confusion about what could be an optimal approach. There is also little data on the efficacy of different treatments for RP-related CME. Various treatments have been proposed, including topical and oral carbonic anhydrase inhibitors (CAIs), nonsteroidal anti-inflammatory drugs, anti–vascular endothelial growth factor (VEGF) agents, laser photocoagulation, and pars plana vitrectomy with peeling of the internal limiting membrane.[5] Among these, CAIs have commonly been considered the first-line treatment. Previous research conducted at our center investigated the efficacy of oral acetazolamide in managing this condition and found it to be effective in improving visual acuity and reducing macular thickness.[6] More recently, intraocular administration of corticosteroids (e.g., by dexamethasone implant) has shown efficacy in small case reports and series.[7–11]

Ozurdex (Allergan Inc, Irvine, CA) is a biodegradable intravitreal implant, designed to provide sustained delivery of dexamethasone to the retina over a period of several months, with the aim of reducing inflammation and improving visual acuity. Previous studies have shown that Ozurdex is effective and safe for the treatment of macular edema secondary to vascular diseases, and for CME in an inflammatory setting, such as noninfectious uveitis and postoperative inflammation.[12,13]

The aim of this prospective, paired-eye pilot study was to compare the efficacy and safety of two treatments for RP-related CME, IVDI and topical CAIs, over a period of at least 12 months.

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Ozurdex (Allergan Inc, Irvine, CA), a biodegradable intravitreal implant, is not labeled for the use discussed here.

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Materials and Methods

In this 12-month prospective, paired-eye, pilot study, patients with RP complicated by bilateral CME were enrolled and followed up in our retinal outpatient clinic, ASST Santi Paolo e Carlo Hospital, member of the European Reference Network for Eye Diseases, from July 2020 to December 2022.

The diagnosis of RP was based on typical fundoscopy, full-field electroretinographic patterns, and visual field constriction and was confirmed by genetic analysis, if available.

The inclusion criteria were as follows: age >18 years, presence of bilateral CME secondary to RP (CMT > 300 μm), absence of any other eye disease that could cause CME, cataract surgery performed at least 6 months before the baseline visit, and suspension of any topical or systemic drugs that reduce CME at least 1 month before baseline visit. Evidence of ocular hypertension or glaucoma was an exclusion criterion.

The primary endpoint was a difference in CMT and macular volume as evaluated by spectral-domain optical coherence tomography between the two treatments at every time point. Secondary endpoints were changes in visual acuity, central retinal sensitivity, and intraocular pressure (IOP) fluctuations at every time point.

At baseline, a clinician performed a comprehensive ophthalmologic examination including: best-corrected visual acuity (BCVA), anterior segment evaluation, IOP (by Goldmann applanation tonometry), dilated fundus ophthalmoscopy, central visual field and spectral-domain optical coherence tomography. Eligible patients were then recruited for the study. One eye, randomly chosen, was treated with IVDI and the contralateral eye was treated with topical CAI (dorzolamide) three times a day.

At days 1 and 7, fundoscopy was repeated to exclude adverse intraocular events, and IOP changes were recorded. Scheduled visits, as described above, were performed at months 1, 3, 6, 7, 9, and 12. If CME persisted at 6 months or recurred with CMT > 300 μm, a second IVDI was considered in the same eye. The fellow eye continued with topical CAIs for the 12-month duration of the study.

The study complied with the Declaration of Helsinki and international guidelines. The study protocol was fully approved by the ethics committee of Milan Area 1 (protocol number 39379/2019).

Spectral Domain Optical Coherence Tomography

Cystic macular edema was assessed by scans obtained with a Spectralis spectral-domain optical

coherence tomography (Heidelberg Engineering, Heidelberg, Germany). We collected a single-line horizontal scan 30° across the fovea (average of 100 images), using automatic eye-tracking software and multiple-line scans (97 horizontal lines, area 20° × 20°, 512 images averaged per scan). Baseline single and multiple-line scans were used as reference for new readings at each follow-up examination.

Central macular thickness was measured by a single scan across the fovea. Macular volume was measured in the subcentral field of the Early Treatment Diabetic Retinopathy Study grid.

Central Visual Field Analysis

At each visit, visual field tests were assessed using Compass fundus-tracking perimetry (CMP; CenterVue, Padua, Italy), an automated perimeter equipped with an eye tracker and a scanning ophthalmoscope. We used a 10-2 grid, strategy 4-2, to collect retinal sensitivity changes of the posterior pole, aiming to explore correlations between structural and functional changes.

A new examination was performed at baseline, then a follow-up examination was performed at each time point to ensure that the same retinal locations were tested. We evaluated mean sensitivity within the central 10° and 5° from fixation at every time point. We defined the central 10° sensitivity as "perimetric sensitivity" and the central 5° sensitivity as "central perimetric sensitivity."

Dexamethasone Implant

After topical anesthetic, all injections were performed by the same operator (L.C.) through pars plana using a customized, single-use 22-gauge applicator under standard sterile conditions.

Statistical Analysis

Linear mixed models were used to compare the two treatments at different time points for CMT, macular volume, BCVA, perimetric sensitivity, and IOP. Central macular thickness and macular volume were log_{10} transformed before analysis. The same models were used to compare each time point with its baseline. The fixed effects included an interaction term between the treatment and the month of follow-up (treated as a discrete factor).

Results

Nine patients (5 men and 4 women) with bilateral RP-related CME were recruited for the study and were followed for 12 months. The mean age of patients at baseline was 42.1 years (range 23–70 years). Mean CMT at baseline was 518.44 ± 127.44 μm in eyes treated with topical CAIs and 554.22 ± 137.84 μm in eyes treated with IVDI ($P = 0.5393$); mean macular volume at baseline was 500 (107.07) μm and 530.89 (115.7) μm, respectively. Mean BCVA at baseline was 0.47 ± 0.24 logarithm of the minimum angle of resolution (20/59) in topical CAI-treated eyes and 0.49 ± 0.30 logarithm of the minimum angle of resolution (20/62) in IVDI-treated eyes ($P = 0.7229$). Mean CMT thickness, mean macular volume, and mean BCVA at each time point are shown in Table 1.

Two eyes of two patients treated with IVDI at baseline developed ocular hypertension (>30 mmHg) 1 month after injection and were therefore excluded from possible re-treatment. At month 6, seven eyes randomized for IVDI were re-injected, one of which developed ocular hypertension (>25 mmHg) after the second injection. All three cases of ocular hypertension were treated with a topical fixed combination of 0.1% brimonidine/0.5% timolol twice a day, bringing IOP to <20 mmHg within 3 months.

There was a significant difference in CMT between the two treatments at months 1 and 7 (Table 1 and Figure 1). Both eyes showed a similar trend in CMT, but the change was significantly different from baseline only for eyes treated with IVDI at month 1 ($P < 0.0001$), month 3 ($P = 0.0017$), and month 7 ($P < 0.0001$) and borderline significant ($P = 0.0510$) for eyes treated with dorzolamide at month 7.

The same results were obtained for macular volume: a significant difference in macular volume was observed between the two treatments at months 1 and 7 (Table 1).

Best-corrected visual acuity was significantly better than baseline at month 3 ($P = 0.0165$), month 7 ($P = 0.0387$), month 9 ($P = 0.0064$), and month 12 ($P = 0.0043$) for eyes treated with CAI, whereas it did not show any significant change at any time point for eyes treated with IVDI. Comparing the treatments, mean BCVA was better in eyes treated with topical CAI at month 12 (borderline significant $P = 0.0510$).

There was no difference in perimetric sensitivity or central perimetric sensitivity between the two treatments at any time point.

We finally explored the correlation of log_{10}(CMT) over time between the two eyes according to the treatment received, to assess whether IVDI treatment in one eye could affect the fellow eye. The CMT of the eye treated with topical CAI was the independent variable. Random intercepts and slopes modeled the trend for each subject. This relationship was positive and significant ($P = 0.0381$), indicating an effect of IVDI on the fellow eye (Figure 2).

Table 1. Longitudinal Study Data

Month	Central Macular Thickness (μm)			Macular Volume (μm)			IOP (mmHg)		
	Dorzolamide	Ozurdex	P	Dorzolamide	Ozurdex	P	Dorzolamide	Ozurdex	P
0	518.44 (127.44)	554.22 (137.84)	0.5393	500 (107.07)	530.89 (115.7)	0.4590	12.89 (1.83)	12.33 (1.8)	0.7172
1	471.56 (152.68)	368.33 (112.79)	**0.0320**	446.62 (124.49)	342.5 (95.62)	**0.0023**	11.89 (1.27)	18.89 (7.93)	**<0.0001**
3	450.43 (139.05)	396.57 (100.23)	0.3545	488.6 (91.83)	420 (66.71)	0.3382	11.88 (1.36)	14.12 (6.33)	0.2380
6	514.12 (151.06)	560.25 (89.25)	0.2901	500.62 (133.57)	521.62 (80.14)	0.4459	11.89 (1.83)	12.33 (1.5)	0.7719
7	432.14 (152.7)	317.29 (110.58)	**0.0129**	466.67 (112.5)	332.67 (86.82)	**0.0017**	10.71 (1.7)	16 (4.93)	**0.0010**
9	472.12 (141.42)	479.38 (120.37)	0.8176	461.12 (121.49)	456.75 (91.9)	0.9649	10.62 (1.41)	12.25 (3.33)	0.1946
12	458.86 (188.17)	517.14 (176.17)	0.1870	456.29 (152.48)	489 (138.98)	0.2883	11.29 (1.8)	12.14 (2.12)	0.5299

Month	BCVA (LogMAR)			Perimetric Sensitivity (dB)			Central Perimetric Sensitivity (dB)		
	Dorzolamide	Ozurdex	P	Dorzolamide	Ozurdex	P	Dorzolamide	Ozurdex	P
0	0.47 (0.24) [20/59]	0.49 (0.30) [20/62]	0.7229	15.96 (5.89)	15.91 (4.87)	0.7817	24.48 (4.83)	24.74 (3.61)	0.9759
1	0.43 (0.19) [20/54]	0.44 (0.19) [20/55]	0.8591	16.18 (5.12)	15.94 (4.74)	0.7925	24.44 (5.2)	25.2 (4.1)	0.3906
3	0.39 (0.21) [20/49]	0.46 (0.28) [20/58]	0.1671	17.17 (5.85)	17.43 (5.25)	0.9539	25.39 (5.12)	24.11 (3.13)	0.7707
6	0.41 (0.21) [20/51]	0.41 (0.26) [20/51]	0.8696	15.82 (5.78)	15.53 (5.4)	0.6337	24.72 (5.47)	25.24 (4.09)	0.7411
7	0.41 (0.23) [20/51]	0.47 (0.26) [20/59]	0.4057	16.11 (6.11)	15.58 (5.73)	0.4456	24.38 (5.33)	24.27 (4.12)	0.6987
9	0.36 (0.21) [20/46]	0.44 (0.29) [20/55]	0.1793	15.23 (5.89)	15.13 (5.43)	0.9146	24.73 (5.11)	24.81 (3.79)	0.9220
12	0.34 (0.22) [20/44]	0.49 (0.29) [20/62]	0.0510	15.07 (4.81)	15 (4.31)	0.8916	23.75 (5.74)	24.42 (4.23)	0.5333

Numbers in bold identify statistically significant values.
Data are presented as mean (SD).
Snellen visual acuities are reported in square brackets.
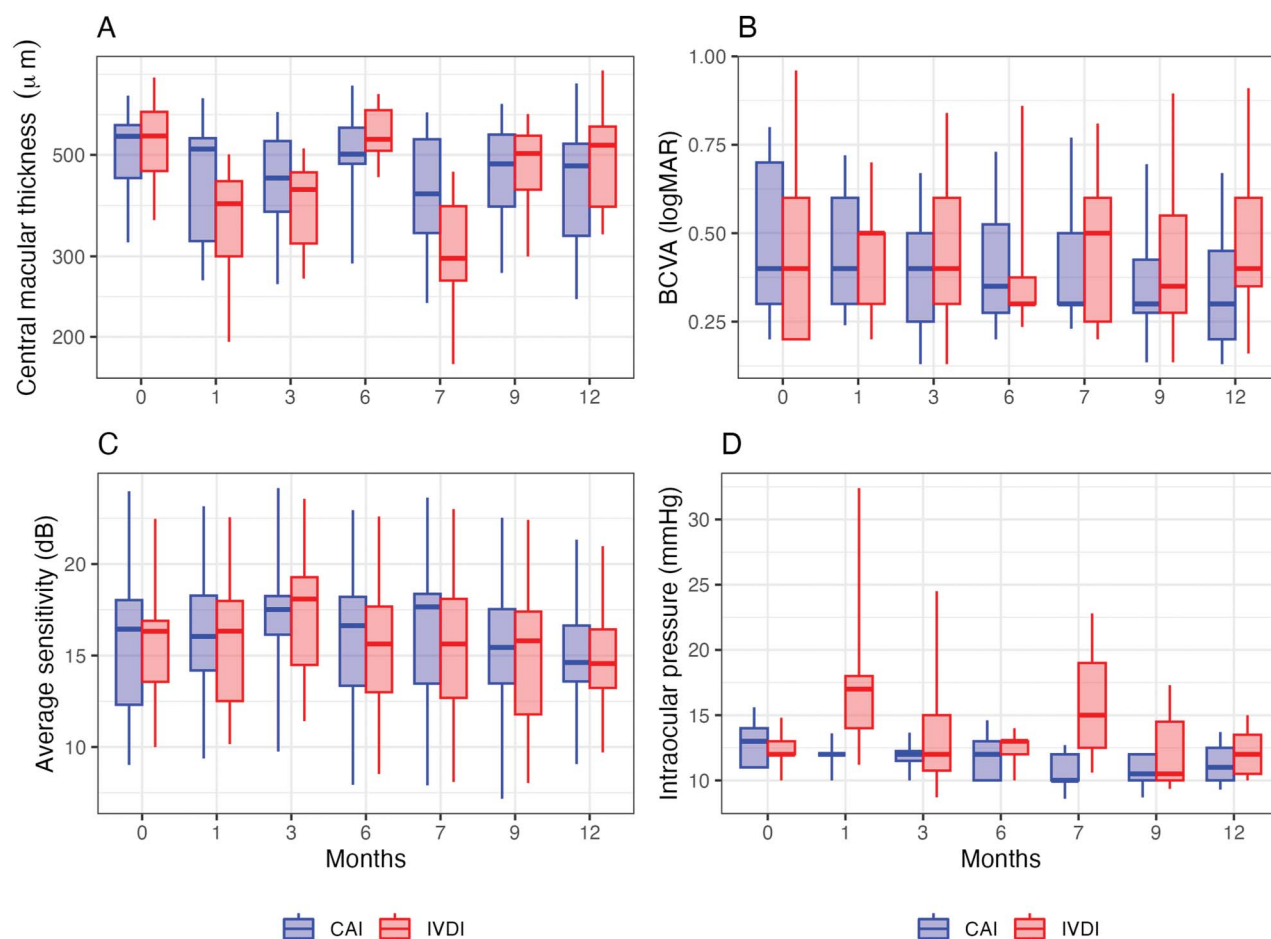LogMAR, logarithm of the minimum angle of resolution.

Fig. 1. Box plots: horizontal line represents median; the box encloses the 25th and 75th percentiles; the whiskers extend from 5th to 95th percentiles.

Discussion

Our study compared the treatment of macular edema in patients with RP complicated by bilateral macular edema. The two eyes of the same patient underwent different treatments: IVDI in one eye, randomly chosen; topical CAI three times a day in the other eye.

Other research groups have explored IVDI as a possible treatment of macular edema in RP,[7–11] but the design of our study was different from that of other published research. For example, Park et al[11] compared two different topical CAI treatments in the two eyes of the same subject. However, unlike Park et al, in our study one eye was treated only with IVDI and the other only with topical CAI to limit the effect of confounders. Our design was also meant to provide within-subject comparison of the effect. This is appropriate because it ensures that the two eyes being compared have the same mutation and are likely to be at the same stage of the disease. The choice of administering topical instead of oral CAIs was to enable the two eyes of a given subject to receive two different treatments and also to limit adverse events associated with oral CAIs.

According to the literature, IVDI injection is effective in reducing edema for up to 3 months.[7–11] In fact, all eyes in the IVDI group showed a rebound of macular edema at the 6-month re-evaluation. The follow-up duration of our study was 12 months: at this time point, there was no significant change in CMT from baseline in the IVDI group, in line with Park et al but in contrast with Veritti et al, who report that the reduction in CMT at 12 months remained significant with no more injections than used by us.[10,11]

Topical CAI treatment has been reported in a number of case series, where a 40% to 81% reduction in CMT was observed.[14–16] In our study, a reduction in CMT of borderline statistical significance with respect to baseline was observed at Month 7 assessments in eyes treated with topical CAIs. Interestingly, a CME rebound was observed despite continued treatment with topical CAIs, as reported in previous studies.[17–19] As reported by Shimokawa et al,[20] the main risk factors for CME recurrence seem to be the
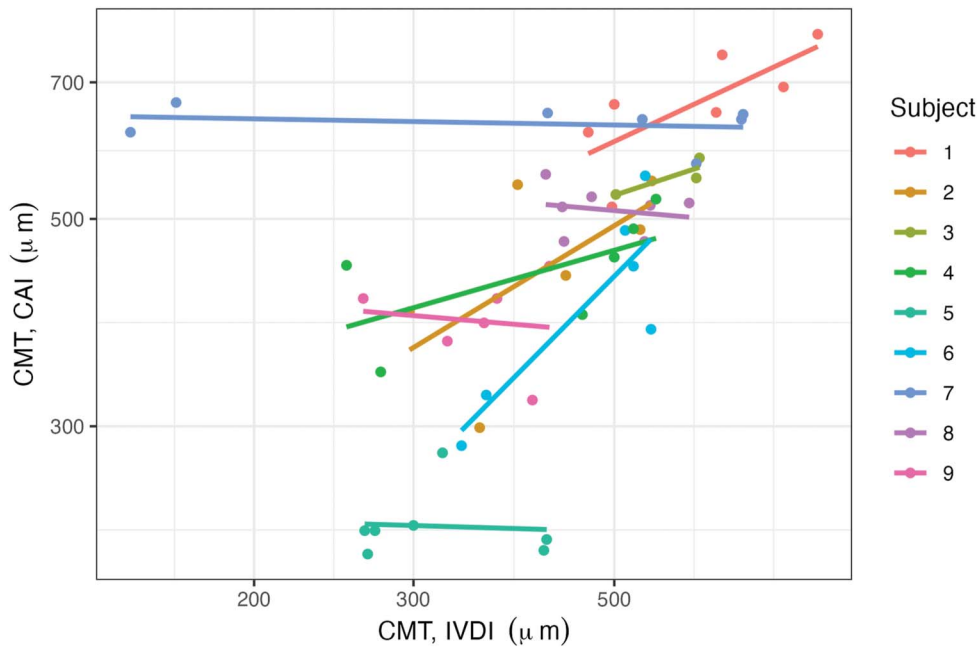
Fig. 2. Within-subject relationship between the CMT of the eye treated with IVDI and the fellow eye treated with topical CAI.

duration of edema and central subfield thickness. In all our patients, we observed a rebound of edema, but because our pilot study concerned a limited number of patients, we were unable to confirm their hypothesis.

Comparing the two treatment groups in CMT reduction, treatment with IVDI proved to be much more effective than topical CAI at the two assessments 1 month after the injections ($P = 0.0320$ at month 1, $P = 0.0129$ at month 7), but at month 12, the difference in CMT between the two treatments was not statistically significant. To the best of our knowledge, ours is the first study to compare these two isolated treatments in two eyes of the same patient.

The BCVA measured at the various time points confirmed that IVDI does not seem to improve BCVA at months 6 and 12. However, unlike previous reports[7–11] demonstrating a positive effect of IVDI on BCVA in the early posttreatment months, the change in BCVA in our IVDI group did not show significant changes at any posttreatment assessment. We postulate that this absence of statistical significance may be because of two factors: (1) the limited number of patients included in the study and (2) the absence of naive patients: all patients enrolled were already monitored at our center and had a history of chronic bilateral macular edema. This probably therefore made them less functionally responsive to CME reduction.

Further support for our results comes from the hypothesis that the pattern of BCVA in patients with RP-related CME is influenced more by outer layer integrity than by CMT.[21–23] In this regard, chronic CME may play a role in disrupting the photoreceptor layers, thus limiting changes in functional metrics. Interestingly, eyes treated with topical CAI showed significant and progressive improvement at all time points except month 1: less fluctuation in CMT and reduced spikes with respect to IVDI treatment suggest a better effect on BCVA. However, this failed to reach statistical significance: the difference in mean BCVA between the two groups showed a borderline P-value, in favor of topical CAI, at month 12.

Administration of IVDI has been reported to improve retinal sensitivity in the central 10° in both eyes in cases of CME secondary to diabetes or central vein occlusion.[24,25] Topical CAI has also been shown to be effective in improving central retinal sensitivity in patients with RP.[15,19] Here we tested whether there could be changes in retinal sensitivity in the central 5° and 10° in eyes with RP-related CME undergoing IVDI. Best-corrected visual acuity alone might not have been able to account for the functional change occurring with reduction of CME. However, retinal sensitivity in the central 5° and 10° did not show any statistically significant differences at the various time points, either between the two treatments or with respect to baseline. We again surmise that the absence of naive patients and the complex changes to the outer retina that occur in RP may have influenced this lack of change in retinal sensitivity.

Whether IVDI in one eye can have an effect on the contralateral eye is still unclear. In our cohort, we observed a positive correlation in the time course of

CME changes between the two eyes in five of nine patients (Figure 3), with an overall significant correlation. Only single case reports in the literature describe an effect on the contralateral eye after unilateral dexamethasone injection in cases of CME secondary to RP, diabetes, noninfectious uveitis, and radiation maculopathy.[26–29] As mentioned above, the etiopathogenesis of RP-related CME is multifactorial, and corticosteroids affect several mechanisms. It may be sufficient for a minimal concentration of corticosteroids to enter the circulation and reach the contralateral eye to obtain an effect on any of these mechanisms (e.g., modulating the low-level chronic inflammation that occurs in RP). On one hand, this may offer an insight into the future development of a treatment, for example, by administering topical steroids instead of IVDI, because a lower concentration of steroids might be sufficient. There seems to be limited data in the literature on topical steroid treatment for RP-related CME.[30,31] Such treatment can be suspended promptly in the case of side effects, such as increased IOP. On the other hand, this finding may indicate that despite its theoretical advantages, a within-subject comparison may not be suitable for investigating the isolated effects of IVDI through comparison of the two eyes. This should be taken into account when planning larger studies.

Limitations of our study include the small statistical sample of patients with chronic bilateral edema, who because of long-standing CME lesions could be less responsive to treatment, and the fact that we compared the two eyes of the same subject when IVDI treatment could affect the contralateral eye. Functionally, differences in visual acuity may have emerged as significant with a larger cohort, although this is unlikely because
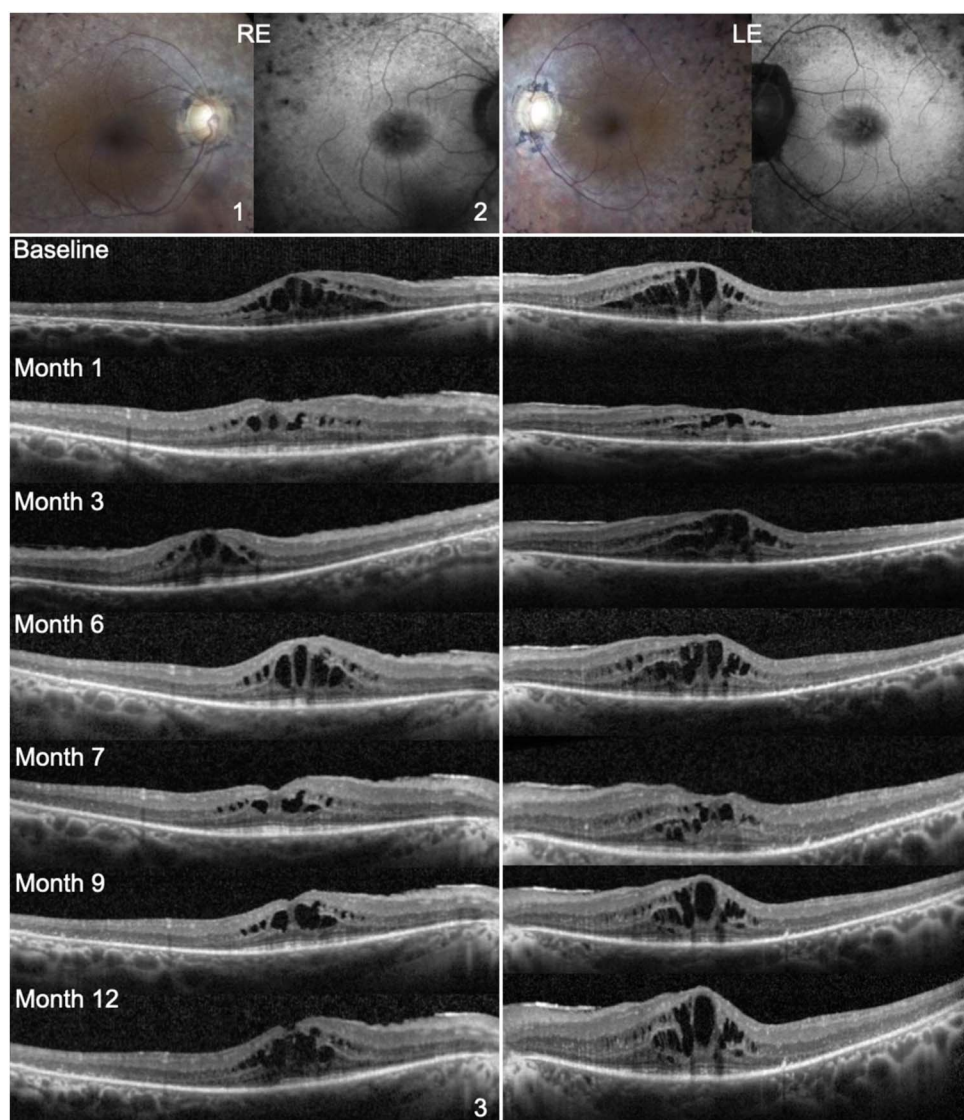

Fig. 3. Example of the possible effect on the fellow eye after unilateral IVDI. Color fundus photography (1) and autofluorescence (2) at baseline. Spectral-domain optical coherence tomography images at various time points (3): IVDI was performed in the left eye (LE) at baseline and after 6-month evaluation. CMT in the LE decreased 1 month after IVDI (months 1 and 7), but then recurred. A similar trend was observed in the right eye (RE), which was treated continuously with topical CAI three times a day, from baseline to month 12.

we did not find any borderline *P*-values and essentially no clinically meaningful differences in average changes of functional metrics. Despite these limitations, our results raise important considerations worthy of further exploration. Intravitreal dexamethasone implant has been demonstrated superior to topical CAI in reducing CME, but its effects wear off within 3 months of implant: this calls for repeated injections, which are not, however, free of side effects, the main one being a rise in IOP, effectively limiting the use of IVDI and its efficacy in practice. To the best of our knowledge, an effect of IVDI injection on the fellow eye has not hitherto been demonstrated in a series of patients undergoing treatment. Although raising safety issues concerning systemic effects, this seems to support the idea that low concentrations of corticosteroids may reduce RP-related CME.

In view of the excellent anatomical response to treatment with IVDI, the different mechanisms of action through which corticosteroids act, and considering that corticosteroids may also help slow the course of the disease,[32] we believe that they may be the most suitable class of molecule for the treatment of RP-related CME. Their routes, timing, and modes of administration are worthy of further study.

Key words: carbonic anhydrase inhibitors, contralateral eye, dexamethasone implant, macular edema, retinitis pigmentosa.

Acknowledgments

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