



# Intravitreal dexamethasone implant concomitant to cataract surgery in retinitis pigmentosa: potential retinal preservation effect

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## ABSTRACT

**Purpose:** To evaluate the potential maintenance of the ellipsoid zone (EZ) by optical coherence tomography (OCT) of retinitis pigmentosa (RP) patients, treated with intravitreal dexamethasone implant at the same time of cataract surgery.

**Design:** In this retrospective cohort study, sixty-two eyes of patients with RP and cataract were enrolled and sorted in two groups.

**Methods:** The first group ("Ozucat" group) included 26 eyes of patients who underwent cataract surgery combined to dexamethasone intravitreal implant (Ozurdex, DEX implant). The second ("cataract alone" group) included 38 eyes who underwent only cataract surgery.

**Main Outcomes Measure:** We evaluated best corrected visual acuity (BCVA) in ETDRS letters and EZ length with retinal structural assessment (OCT).

**Results:** In the Ozucat group, the increase in EZ length from baseline was statistically significant both at 6-months ( $p < 0.0001$ ) and 12-months ( $p < 0.0001$ ) compared to "cataract alone" group. However, no statistical difference in BCVA was highlighted between the two groups.

**Conclusion:** Our study showed that eyes with typical RP, presenting cataract and concomitant signs of retinal inflammation, treated by combined cataract surgery and intravitreal dexamethasone implant, exhibited a maintenance of the EZ integrity, suggesting a potential retinal preservation effect of steroids.

## 1. Introduction

The term Retinitis Pigmentosa (RP) is typically used to define a group of retinal genetic dystrophies, characterized by photoreceptors degeneration and retinal pigmented epithelium (RPE) abnormalities.<sup>1,2</sup> The prevalence of RP is 1/4000.<sup>3</sup> Many aspects of photoreceptors biology can be affected due to a single mutation in any of over 70 recognized causal genes; however, this genetic heterogeneity converges towards similar phenotypes.<sup>4</sup> RP patients usually complain of night blindness

(nyctalopia) as first symptom, since rods are primarily damaged and progressively die out, resulting in a progressive visual field decrease. According to Campochiaro et al., in RP eyes the oxidative damage is the major contributor to cone cell death.<sup>5</sup> Cone photoreceptors are also secondarily involved by the development of local and complex inflammatory reactions, leading retinal microglia to release reactive molecular species which concentrate in the outer retina and that contribute to accelerate the degenerative phenomenon.<sup>6</sup>

Campochiaro et al. reported a reduction in photoreceptor loss in RP

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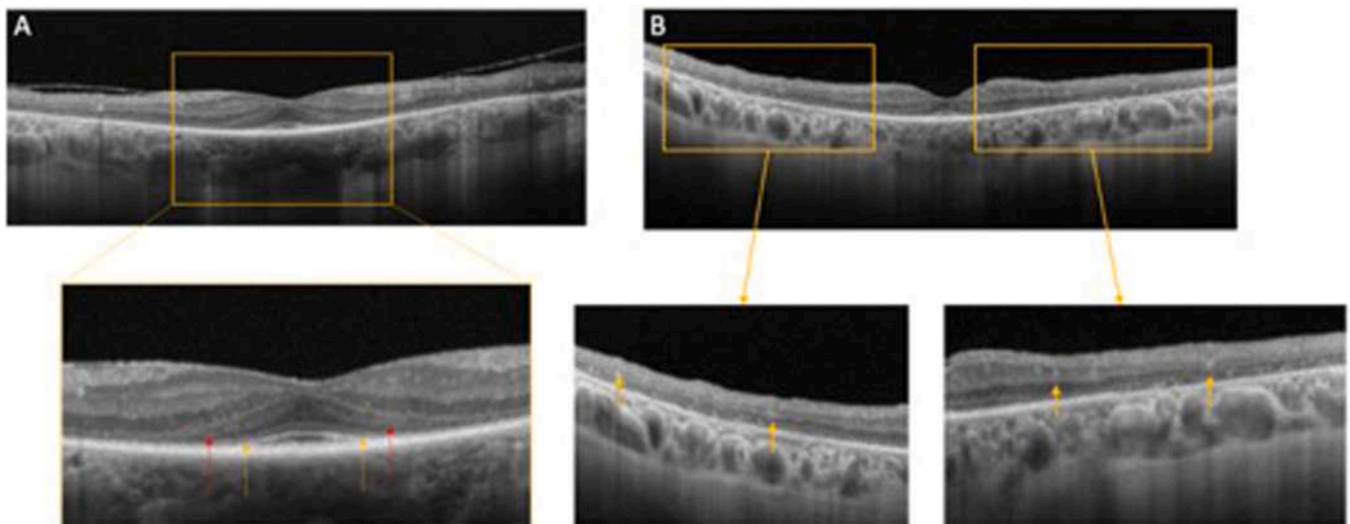
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**Fig. 1.** A) Optical coherence tomography (OCT) scan showed flattening of the foveal depression, disruption of the ellipsoid zone (EZ) and the external limiting membrane (ELM) (yellow arrows), associated with thinning in the outer nuclear layer (ONL) (red arrows). B) OCT showed hyperreflective foci (yellow arrows) as signs of intraretinal inflammation.

animal models treated with antioxidants, although Guadagni et al. observed a significant elevation in pro-inflammatory gene expression in mice with retinal degeneration during the photoreceptor death phase. Guadagni employed dexamethasone to inhibit microglial activity, demonstrating a greater number of cone cells persisted, protecting photopic vision.<sup>7,8</sup> In addition, Barone et al. demonstrated in experimental models of RP that environmental enrichment is a useful and minimally invasive technique for promoting long-lasting retinal protection.<sup>9,10</sup>

The morphological observation of photoreceptor degradation *in vivo* continues to be challenging. This is the reason why, to this day, the most reliable source is the assessment of the visual field and OCT examinations.

One of the recognized structural changes in RP eyes is the circumfoveal ellipsoid zone (EZ) loss and the following disruption of the outer nuclear layer (ONL) in the late stages of the disease.

Attenuation, interruption, and disruption of EZ have been considered reliable predictors of long-term visual impairment. Furthermore, the number of outer retinal hyperreflective foci correlates with intraocular inflammation and photoreceptor degradation in RP.<sup>2</sup>

Patients with retinitis pigmentosa may gain advantages from cataract surgery; however, a comprehensive preoperative assessment and surgical proficiency are essential to mitigate potential consequences. Visual outcomes are contingent upon postoperative management and monitoring. Moreover, early cataract surgery can improve quality of life; nevertheless, RP patients often require specialized procedures.<sup>11</sup>

In Fig. 1, the foveal depression became flatter, EZ stopped working, and the external limiting membrane (ELM) was linked to the thinned out ONL and the presence of hyperreflective foci (HRF).

Our study aimed to evaluate, using OCT scans, the potential maintenance of the EZ in RP patients treated with intravitreal dexamethasone implant and cataract surgery.

## 2. Materials and methods

This retrospective cohort study was conducted at the Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy. The study was approved by the Catholic University/Fondazione Policlinico Universitario A. Gemelli IRCCS Institutional Ethics Committee (protocol ID number: 3860). A signed informed consent was obtained by each enrolled patient, after a full explanation of the target protocol. The study was carried out in conformity to the Declaration of Helsinki. Patients

with typical RP, confirmed by genetic testing, cataract and retinal inflammatory signs were enrolled.

Two groups were considered: the first ("Ozucut" group) included eyes of patients who underwent cataract surgery combined with dexamethasone intravitreal implant (Ozurdex, DEX implant). The second ("cataract alone" group) included patients who underwent only cataract surgery without additional procedures.

RP diagnosis was confirmed by genetic testing.

Only patients who underwent a complete ophthalmological evaluation at baseline, 6-months and 12-months follow up were included in the study.

Exclusion criteria were pseudophakia, previous vitreoretinal surgery, glaucoma, myopia or hyperopia  $\geq 3.0$  diopters, uveitis, presence of macular edema or schisis before or after surgery, OCT image quality lower than 7/10.<sup>12</sup>

### 2.1. Procedures and instruments

All patients underwent a complete preoperative ophthalmological examination, including best corrected visual acuity (BCVA) according to the Early Treatment for Diabetic Retinopathy Study (ETDRS), slit lamp and fundus examination. Furthermore, multimodal imaging was performed, comprehensive of fundus autofluorescence (FAF), color fundus retinography (CFP), retinotomography (RM) imaging and OCT. In the Ozucut group, intraocular pressure (IOP) was assessed using the Goldmann applanation tonometer at 1 month, 3 months, 6 months and 12 months follow up.

To assess the residual EZ-extension, high-definition 5-line raster and  $6 \times 6$  mm macular cube  $512 \times 128$  scans procedures were conducted using OCT (Cirrus HD-OCT 5000 with AngioPlex software, version 10.0; Carl Zeiss Meditec, Jena, Germany). All B-scans were acquired in follow-up modality.

Two separate blinded expert examiners (V.C. and E.D.A.) manually measured the EZ length on OCT scans at baseline, i.e. the pre-operative status, at 6 months and 12 months after the surgical procedure. The consensus agreement (Cohen coefficient agreement) was considered suitable only if  $> 0.9$ . The EZ width was specifically measured at the retinal locations where the temporal and nasal EZ boundaries converged in the RPE, without possibility to discern. If the EZ resulted absent, a value of 0 was assigned and defined as unmeasurable EZ.

In addition, we distinguished the two groups into measurable EZ and unmeasurable EZ.

**Table 1**  
Demographical and clinical data of both analyzed groups

Variables	Ozucat Group	Cataract Alone Group
Number of patients	26	38
Age (mean $\pm$ SD)	55.53 $\pm$ 14.13	54.26 $\pm$ 14.53
Female/Male	8/18	14/24
Visual Acuity -ETDRS letters (Baseline)	38.12 $\pm$ 34.36	50.31 $\pm$ 30.39
Visual Acuity- ETDRS letters (6-month Post Surgery)	50.31 $\pm$ 29.85	51.84 $\pm$ 31.36
Visual Acuity - ETDRS letters (12-month Post Surgery)	50.88 $\pm$ 29.45	53.02 $\pm$ 31.17
EZ length - $\mu$ m (Baseline)	2810.34 $\pm$ 2835.58	2880.10 $\pm$ 1906.66
EZ length - $\mu$ m (6-months Post Surgery)	2958.80 $\pm$ 2942.15	2768.02 $\pm$ 1884.27
EZ length- $\mu$ m (12-month Post Surgery)	2965.92 $\pm$ 2949.49	2766.81 $\pm$ 1884.50

SD = standard deviation; EZ = ellipsoid zone

We included in the study only one eye for each patient. In patient with bilateral surgery only one eye was randomly selected.

## 2.2. Genetic testing

Blood or saliva samples were collected from the study subjects, and DNA extraction was performed using a commercial kit (E.Z.N.A. Blood DNA kit, Omega Bio-Tek Inc., Norcross, GA, USA).

The NGS analysis of DNA samples was carried out using an Illumina MiSeq personal sequencer (Illumina, San Diego, CA, USA), in conjunction with an in-house bioinformatics pipeline used for variant calling and annotation, as previously described.

To validate the identified genetic variants, Sanger sequencing was performed using a Beckman Coulter CEQ 8000 sequencer (Beckman Coulter, Milan, Italy). This sequencing method was also employed for family segregation studies when additional family members were available, enabling a more comprehensive understanding of the

inheritance patterns of the identified variants.

A comprehensive search for variants was conducted using multiple databases, including the Leiden Open Variation Database (LOVD), dbSNP (<https://www.ncbi.nlm.nih.gov/snp/>), ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>), and gnomAD (<https://gnomad.broadinstitute.org/>). The pathogenicity of the identified variants was assessed according to the guidelines set forth by the American College of Medical Genetics and Genomics (ACMG)<sup>14</sup>, with the support of the online tool VarSome (<https://varsome.com/> accessed on May 2023).

Multiplex ligation-dependent probe amplification (MLPA) was used to analyze gene rearrangements for the detection of whole-gene or intragenic rearrangements of specific genes such as *ABCA4*, *EYS*, *RP2*, *PCDH15* and *USH2A*, following the manufacturer's instructions ([www.mrc-holland.com](http://www.mrc-holland.com)), and analyzed using the Beckman Coulter CEQ 8000 sequencer (Beckman Coulter, Milan, Italy).

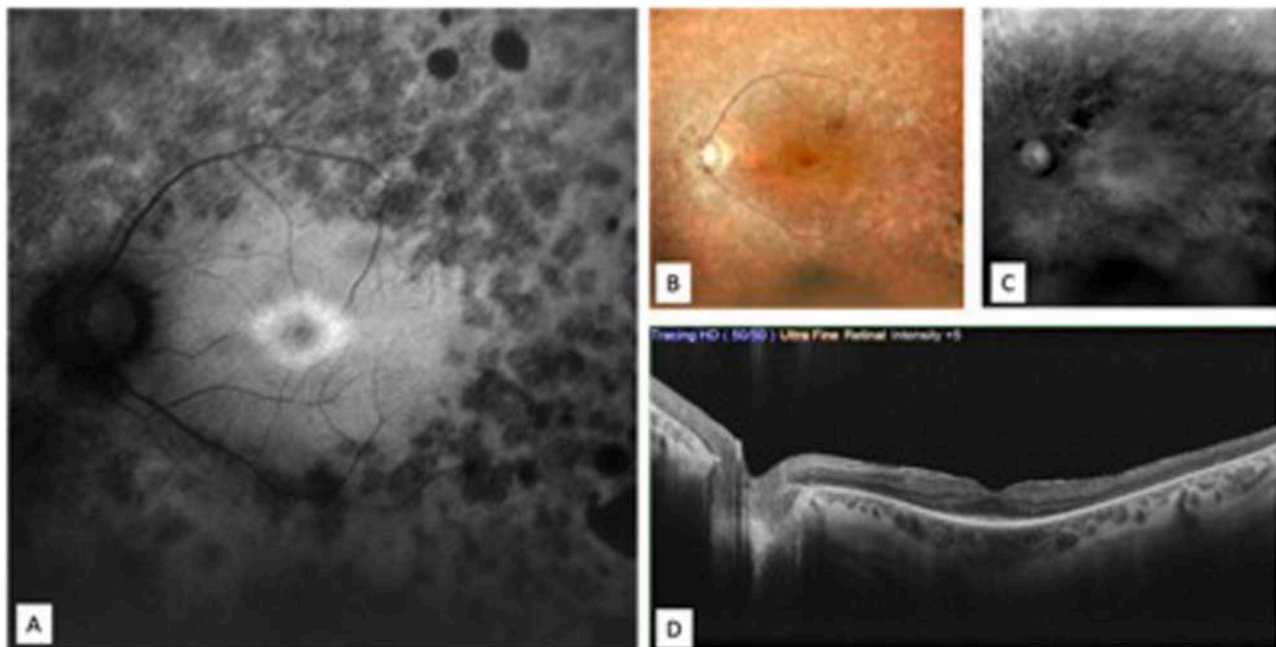
Prior to the genetic testing procedure, all patients underwent genetic counseling to gather family history and pedigree information.

## 2.3. Statistical analysis

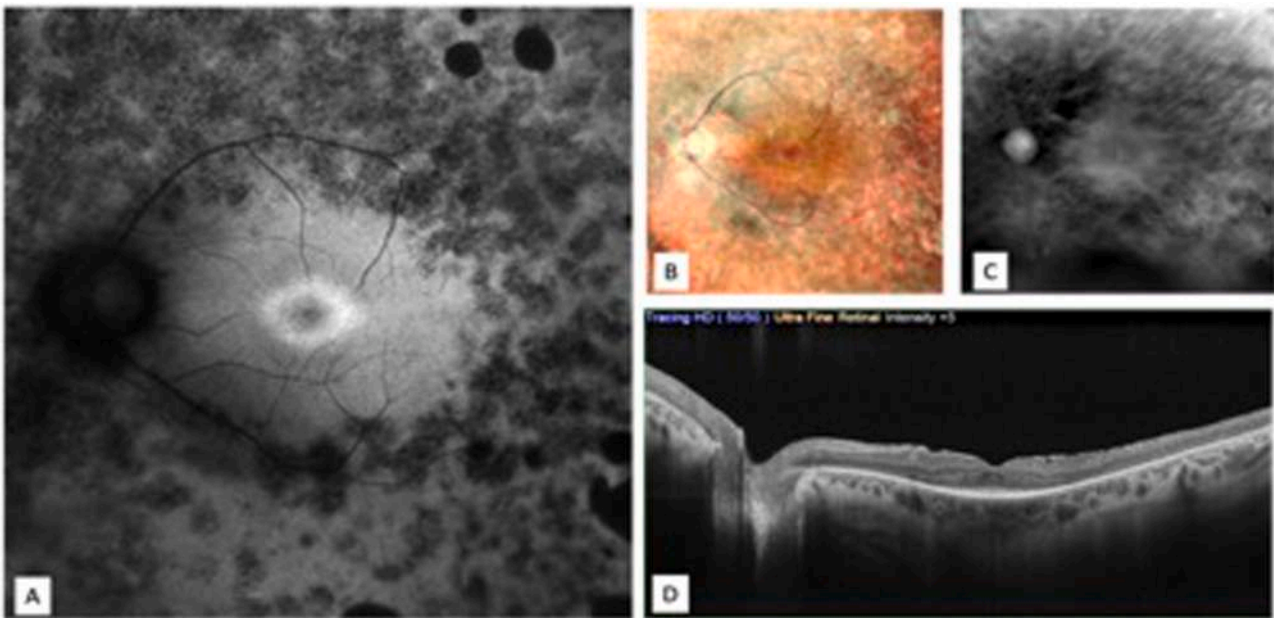
Results were assessed using non-parametric statistics because of the data distribution. The evaluation within individuals was conducted using the Wilcoxon matched-pair test, whereas intergroup analysis assessing postoperative alterations in OCT parameters and visual acuity was performed using the Mann-Whitney and Wilcoxon tests. Alterations in OCT parameters from baseline were represented as a percentage (i.e., (post-surgical value - baseline value)/baseline value  $\times$  100). Differences in BCVA (ETDRS letters) were computed by subtracting baseline values from post-surgical values. Wilcoxon's test was utilized to assess statistical significance within the same group throughout follow-up. A p-value of less than 0.05 was considered statistically significant for all analyses.

## 3. Results

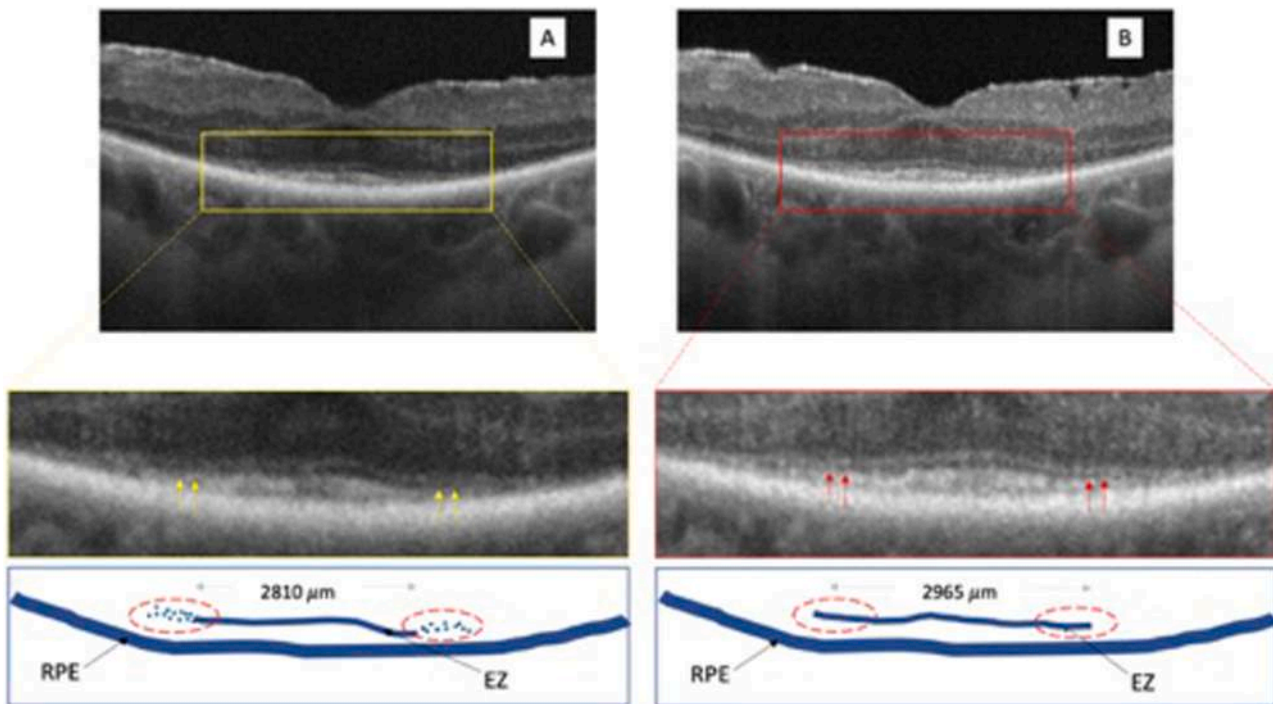
Sixty-four eyes of 64 patients who suffered from RP and cataract



**Fig. 2.** Multimodal imaging in a retinitis pigmentosa (RP) patient prior to cataract surgery and intravitreal dexamethasone implantation. A) Fundus autofluorescence (FAF) showed RPE changes involving the middle retinal periphery reaching the vascular arcades, thin vessels and hyperautofluorescent circular area in the fovea. B) Color fundus photography showed the bones spicules, pale optic disc, thin vessels, changes in the foveal reflex. C) Retromode imaging did not show any prominent lesions and greyish macular flattening. D) Optical coherence tomography (OCT) B-scan showed irregular retinal profile, with ellipsoid zone (EZ) loss except for the foveal region, external limiting membrane (ELM) loss and thinning of the outer nuclear layer (ONL).



**Fig. 3.** Multimodal imaging in the same retinitis pigmentosa patient depicted in Fig. 2, after cataract surgery and intravitreal dexamethasone implant. A) Fundus autofluorescence (FAF) showed RPE changes involving the middle retinal periphery reaching the vascular arcades, thin vessels and hyperautofluorescent circular area in the fovea stable compared to previous examination. B) Color fundus photography showed the bones spicules, pale optic disc, thin vessels, changes in the foveal reflex. C) Retromode imaging did not show any prominent lesions and greyish macular flattening. D) Optical coherence tomography (OCT) B-scan showed irregular retinal profile, with ellipsoid zone (EZ) loss except for the foveal region, which resulted preserved at follow up, external limiting membrane (ELM) loss and thinning of the outer nuclear layer (ONL).



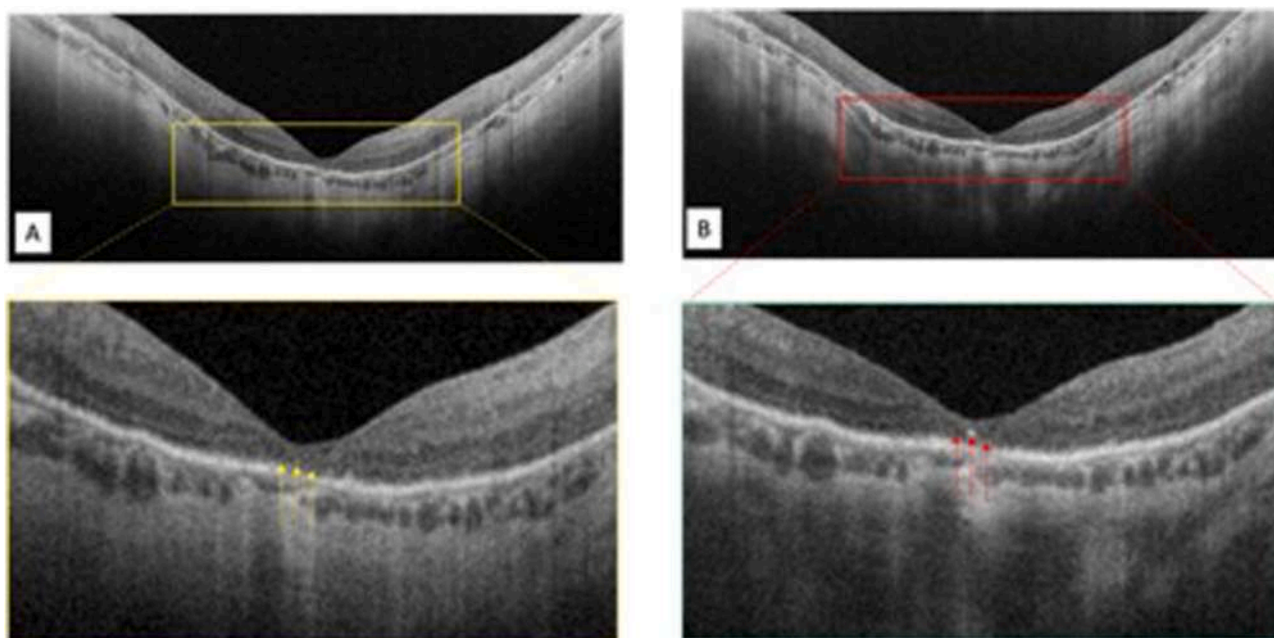
**Fig. 4.** Optical Coherence Tomography (OCT) B-scan of a retinitis pigmentosa (RP) patient before (A) and after (B) combined cataract surgery and Ozurdex implant. Details of the ellipsoid zone (EZ), reporting its length before (yellow arrows) and after combined surgery (red arrows) were evident in the zoomed images.

were enrolled (Table 1). In our study design, 26 out of 64 RP patients were included in the “Ozucut” group, whose mean age was  $55.53 \pm 14.13$  years, and 69.23% were males (Female:Male 8/18). The remaining 38 patients were assigned to the “cataract alone group, whose mean age was  $54.26 \pm 14.53$  years and 63.15% were males (Female:Male 14/22).

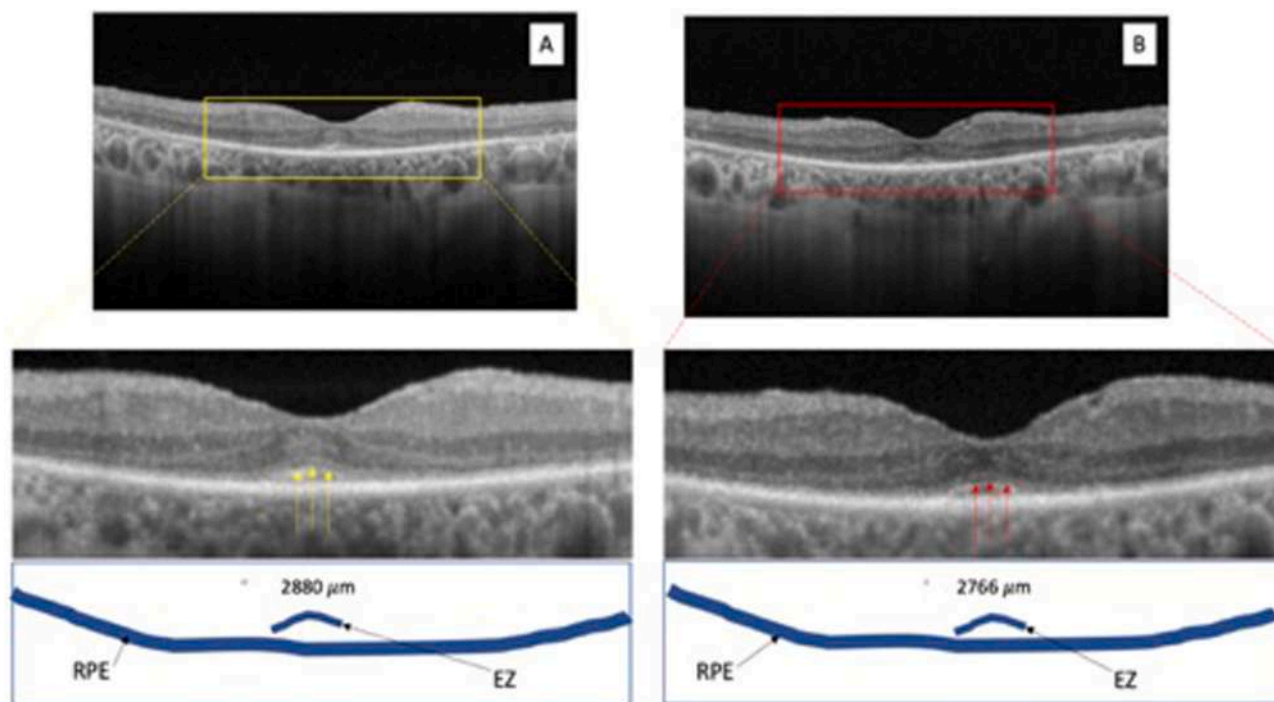
In the Ozucut group, the IOP measurement never exceeded the value of 21 mmHg at 1 month, 3, 6 and 12 months of follow up.

Figs. 2 and 3 showed the multimodal Imaging in a RP patient before and after performing cataract surgery and intravitreal dexamethasone implant.

At baseline, EZ length was  $2810.34 \pm 2835.58 \mu\text{m}$  in “Ozucut” group



**Fig. 5.** Optical Coherence Tomography (OCT) B-scan of a retinitis pigmentosa (RP) patient before (A) and after (B) only cataract surgery. The ellipsoid zone (EZ) remained apparently stable before (yellow arrows) and after (red arrows) the procedure, as represented schematically with a blue line drawing.



**Fig. 6.** High resolution Optical Coherence Tomography (OCT) B-scan of retinitis pigmentosa (RP) patient before (A) and after (B) combined cataract surgery and intravitreal dexamethasone implant. The absence of a measurable EZ-length was evident at baselined (yellow arrows) and remain unchanged after surgery (red arrows).

while at 6 months post-surgery EZ length was  $2958.80 \pm 2942.15 \mu\text{m}$ . At 12-months follow up, the "Ozucat" group showed a median value of 3085 microns EZ length. A statistically significant difference in EZ width between baseline and 6 and 12 months follow up was observed ( $p=0.001$ ) These findings could be appreciated in the high-resolution images of a representative "Ozucat" patient, shown in Fig. 4.

Regarding the "cataract alone" group, the EZ length was  $2880.10 \pm 1906.66 \mu\text{m}$  at baseline,  $2768.02 \pm 1884.27 \mu\text{m}$  at 6 months after

surgery and  $2766.81 \pm 1884.50 \mu\text{m}$  at 12 months of follow up, with no statistically significant difference ( $p=0.73$ ).

Any change was found in the EZ length in patients with no detectable EZ at baseline in both "cataract alone" (Fig. 5) and "Ozucat" groups (Fig. 6).

A schematic representation of our findings was shown in Fig. 7.

Patients with undetectable EZ were not considered in the intergroups analysis, according with Nakamura.<sup>15</sup> Eighteen cases with