

Fig. 7. (a). Representation of a healthy retina, detailing the outer retinal layers (ORL) and the retinal pigmented epithelium (RPE). (b) is representative of a retinitis pigmentosa (RP) patient, in which the ellipsoid zone (EZ) before surgery is missing. No changes are recorded after surgery (b'). (c-c') are representative of a RP patient, included in the cataract group, before and after surgery respectively. No changes in the EZ length can be appreciated. (d-d') are representative of a RP patient, included in the Ozucat group, before and after surgery respectively. In (d), the granularity of the EZ corresponds to photoreceptors maintenance, which results into an increase in the EZ length after combined surgery (d').

indeterminable measurement of EZ were identified. Nine cases of them were in the "Ozucat" group and 9 in the "cataract alone" group. A statistically significant difference was observed between the two groups of patients with quantifiable EZ at both 6 and 12 months follow up ($p < 0.0001$), as shown in Fig. 8.

In the "Ozucat" group, mean BCVA was 38.12 ± 34.36 ETDRS letters at baseline, 50.31 ± 29.85 ETDRS letters at 6 months after surgery and 50.88 ± 29.45 at 12-month follow up.

In the "cataract alone" group, mean BCVA at baseline was 50.31 ± 30.39 ETDRS letters, at 6-month and 12-month follow up it was 51.84 ± 31.36 and 53.02 ± 31.17 ETDRS letters, respectively.

The increase in BCVA was statistically significant for both the "Ozucat" group and "cataract alone" group at 6 and 12 months after surgery ($p = 0.003$).

However, there is no statistical difference between the two groups in terms of ETDRS at either 6 month and 12 months, with p-values of 0.7464 and 0.5351, respectively, as shown in Fig. 9.

No patients experienced any adverse events during and after the surgical procedures, such as rupture of the posterior capsule, post-surgical intraocular hypertension, endophthalmitis and IOL opacification.

4. Discussion

Our findings demonstrated that typical RP patients who received combined cataract surgery and intravitreal dexamethasone implant exhibited superior maintenance of the EZ integrity compared to the cataract-alone group. Retinitis pigmentosa (RP) is characterized by the

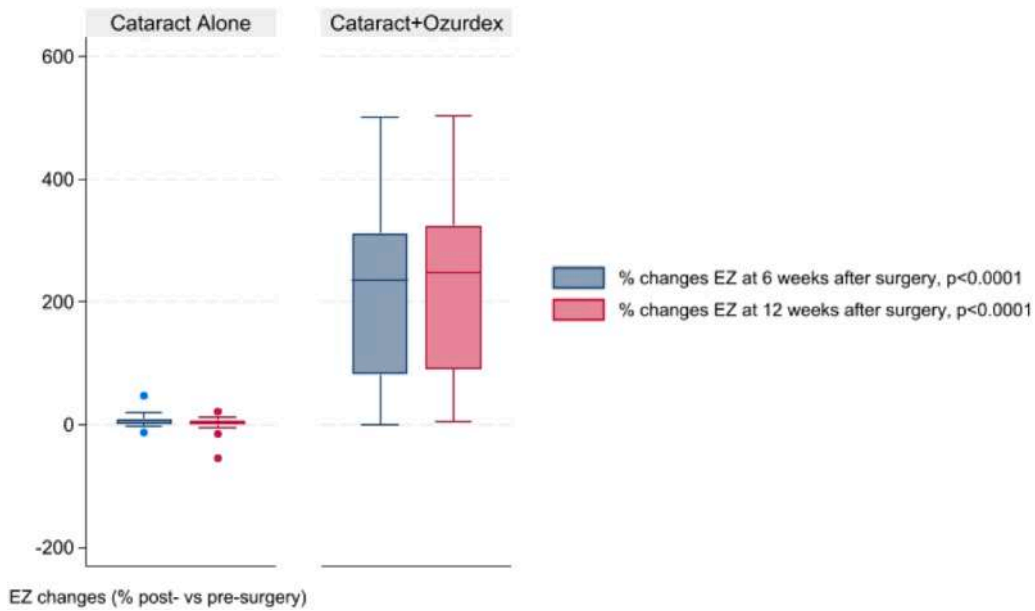


Fig. 8. Box plots of the range of difference for ellipsoid zone (EZ) observed at 6 (blue) and 12 (red) months for both groups. The p values referred to the results of the Wilcoxon test, comparing the changes between the two groups. The horizontal line represented the median, the border the interquartile range (between 25 and 75). The dots were the outliers, beyond the adjacent lines (1.5 IQR).

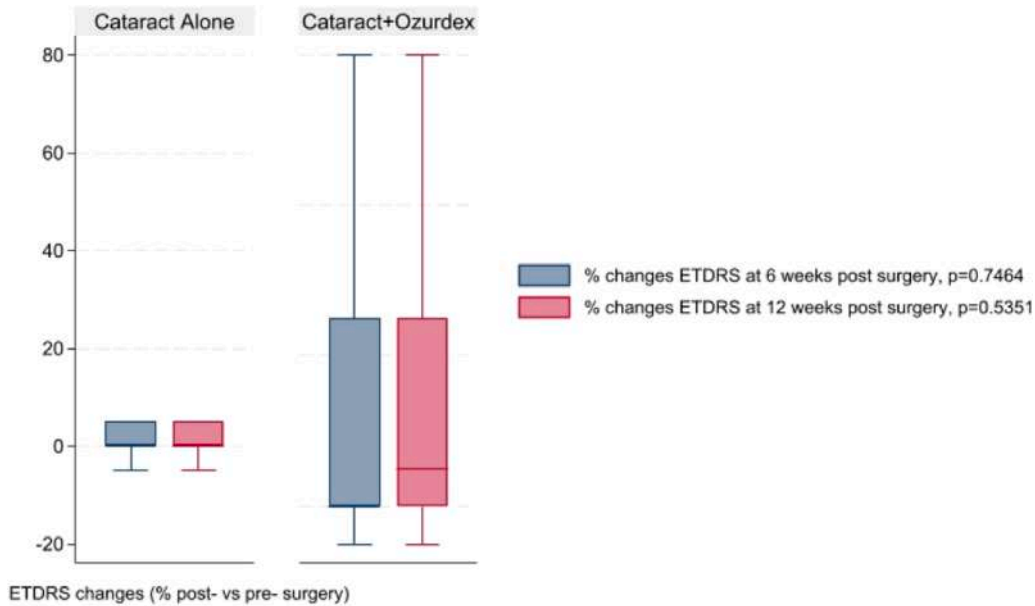


Fig. 9. Box plots of the range of difference for ETDRS observed at 6 (blue) and 12 (red) months for both groups. The p values referred to the results of the Wilcoxon test, comparing the changes between the two groups. The horizontal line represented the median, the border the interquartile range (between 25 and 75). The dots were the outliers, beyond the adjacent lines (1.5 IQR).

degeneration of rod photoreceptors, resulting in a loss of survival factors, which subsequently leads to metabolic failure and morphological alterations in cone photoreceptors. Furthermore, the inflammation exacerbates oxidative stress, modifies the pentose phosphate pathway, and results in cone cell death.

Colombo et al. reported that in RP patients, the EZ width reduced at an annual average rate of 76.4 μm (4.16% per year).¹³ The European Medicines Agency (EMA) recommends the intravitreal dexamethasone implant for adult ocular posterior segment inflammatory disorders.

While both groups had an enhancement in BCVA, only the group receiving the simultaneous Ozurdex implant displayed a statistically significant preservation of the EZ at the 6 and 12-month follow-up. The

potential rationale for the enhanced preservation of EZ in this cohort may stem from the beneficial impact of dexamethasone in mitigating the remodeling and degranulation of impaired cones subsequent to extensive adjacent rod cell death. Nonetheless, the study's retrospective design and limited sample size necessitate additional research to validate our core findings. The absence of post-surgical alterations in eyes with completely compromised ellipsoid zones (EZ length = 0) at baseline indicated the ineffectiveness of intravitreal dexamethasone implants when cone cells had already degenerated or their regressive remodeling was excessively advanced, specifically with damaged inner segments. Furthermore, a recent research by He et al. indicated that there was no enhancement in visual acuity among RP patients post-

cataract surgery when the EZ was not visible in the pre-operative OCT assessment. Based on these data, the authors advised against undergoing surgery when the EZ was undetectable at baseline.¹⁴

Our findings were in line with the concept of bystander degeneration of cones in RP and with the long-time sparing of the most central part of the retina, where cones are relatively isolated from rods. As observed by Guadagni et al., a link existed between retinal inflammation and bystander cone degeneration, reinforcing the notion that cone survival in RP can be pursued using long-lasting anti-inflammatory implants.⁸ Dexamethasone indeed is known to inhibit microglial production and the release of inflammatory molecular species, reducing their toxic effect on cones' survival.

Recently, it has been reported that the first cones' response to an oxidative environment was represented by loss of function, thus followed by death, if the trigger agent was not removed.^{15,16} Chrysostomou et al., demonstrated a decrease in cone b-wave amplitude in the P23H rat, a model of RP, when exposed to a photopic environment, without changes in cone density, but with evidence of a shortening of cone outer segments.¹⁵ On the other hand, exposure for 5 weeks to scotopic conditions elicited a recovery in both cone b-wave amplitude and cone outer segments length.¹⁵ Sahel et al. clearly demonstrated an opposite trend in cone loss and in retinal morphology after the subretinal injection of RdCVF (Rod-derived Cone Viability Factor) protein compared to untreated controls.¹⁷ These results suggested that a step-by-step process leads to cone loss in RP, which begins with outer segment shortening, as reported in various models of this disease.¹⁷

On the other hand, dexamethasone could act directly on cone physiology by modulating their metabolism. Although the regulation of metabolism by corticosteroids at organismal level has already been well characterized, studies at cellular levels are recently emerging. As ligands, these molecules explicit their function by binding to mineralocorticoids (MR) and glucocorticoids receptors (GR) which can control the expression of different immune and metabolic genes.^{18,19} In particular, activated GRs can regulate the gene expression not only of nuclear but also of mitochondrial DNA, although the consequences of this activity are yet not clarified.²⁰ Low doses of corticosterone, the natural corticosteroid, have positive effects on mitochondrial function in cultured neurons by increasing the rate of energy production and calcium holding capability.²¹ Thus, a potentiated mitochondrial activity could optimize the compromised energy yield of cones due to the scarce availability of glucose in RP eyes.

Besides a metabolic amelioration, an additional explanation of the beneficial effects of dexamethasone implant could be from a structural point of view. Recently, it has been demonstrated that the precise organization of cones' mitochondria in the ellipsoid had relevant optical properties to concentrate the light to the outer segments, achieving an effect similar to the Stiles-Crawford one. Hence, active and spatially well-organized mitochondria may improve the visual resolution through a better focusing of light to the outer segments.²²

Remarkably, all included patients in the "Ozucut" group did not report any adverse event related to the combined surgical procedures, such as ocular hypertension and cystoid macular edema.

The primary limitations of our study were the relatively small sample size, the relatively short follow-up interval, the retrospective analysis of images, which did not allow for a test-re-test measurement, and the potential impact of cataract *per se* on OCT image quality. However, only patients whose exams had a quality index greater than 7/10 were enrolled in order to ensure a sufficient resolution and the possibility of an adequate comparison. Moreover, the variability in EZ measurements could be a result of test-re-test reliability and manual measurement as well as potential anomalies from previous image acquisitions (e.g., photobleaching) that may have contributed to EZ disruption. Yet, our data solicited further longitudinal studies in eyes with RP to confirm the efficacy of intravitreal dexamethasone implant and its applicability on a large scale, considering the total absence of pharmacological tools to constrain the disease.

Our findings suggest a potential role for intravitreal dexamethasone implants in typical RP eyes, as demonstrated by EZ preservation in OCT images; however, further research is necessary.

Author contributions

Conceptualization, M.C.S. and E.S.; methodology, G.P., V.C., and E.D.A.; software, G.P., V.C. and E.D.A.; validation, L.P., C.R.; investigation, E.S., D.N.; resources, E.S. and S.R.; data curation E.S. and C.F.; writing—original draft, M.C.S., C.F., F.G., E.S.; writing—review and editing M.C.S., C.F., D.N., E.S.; visualization, C.F.; supervision, S.R. and B.F.; project administration, M.C.S.; funding acquisition: E.S. and S.R. All authors have read and agreed to the published version of the manuscript.

Table content

A notable structural alteration in retinitis pigmentosa (RP) eyes is the disappearance of the circumfoveal ellipsoid zone (EZ) and the subsequent rupture of the outer nuclear layer (ONL) in the advanced stages of the disease. Attenuation, interruption, and disruption of the EZ have been regarded as trustworthy indicators of long-term vision impairment.

To assess the potential preservation of the ellipsoid zone (EZ) with optical coherence tomography (OCT) in patients with retinitis pigmentosa (RP) who received intravitreal dexamethasone concurrently with cataract surgery.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

None.

Acknowledgments

This work was financially supported by NKFIH, MoH and BMBF under the frame of ERA-NET NEURON (NEURON-066 Rethealthsi). Supported by ERN-Eye to BF and SR.

Data Availability Statement

Publicly available datasets were analyzed in this study. This data can be found here: [https://docs.google.com/spreadsheets/d/1h3Bm2Rnwj9IQPbgbU5Go_rnXt0a6EO3E/edit?usp=share_link&ouid=109332089223879485696&rtopf=true&sd=true].

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Catholic University/Fondazione Policlinico Universitario A. Gemelli IRCCS Institutional Ethics Committee (protocol ID number: 3860, approval date: 03/12/2020).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

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