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Dexamethasone implant with fixed or individualized regimen in the treatment of diabetic macular oedema: six-month outcomes of the UDBASA study

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ABSTRACT.

Purpose: **To evaluate a pro re nata administration of Ozurdex® implant versus a single administration for treating diabetic macular oedema (DME).**

Methods: **This exploratory study is designed as a comparative, multicentre, randomized study with a follow-up of 6 months. Patients with DME were assigned to treatment at baseline either with a single Ozurdex® implant during the entire six-month follow-up (fixed group) or Ozurdex® implant followed by retreatment on an individualized basis (PRN group). Patients were scheduled for monthly evaluation based on assessment of best-corrected visual acuity (BCVA) and optical coherence tomography.**

Results: **Twenty eyes were enrolled to the PRN group, and 22 were included in the fixed group. Following an equally steady, initial gain up to month 1, and maintenance up to month 3, vision started to decline in the fixed regimen group. At 6 months, a difference of 0.11 logMAR in BCVA was observed in favour of the PRN group. Compared to baseline, a significant reduction in retinal thickness was achieved up to month 2, when the fixed regimen group had begun to revert to pretreatment level. At 4 and 5 months, the difference in thickness between the two groups was statistically significant ($p < 0.05$). Mean number of treatments was 1.6 in the PRN group. Both fixed and PRN administration of Ozurdex showed a good safety profile.**

Conclusion: **A personalized treatment with monthly monitoring and retreatment as needed is effective in maintaining functional and anatomical benefits of Ozurdex®.**

Key words: as-needed – dexamethasone – diabetic macular oedema – Ozurdex – pro re nata

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Introduction

Currently, 387 million people globally are affected by diabetes. By 2035, the number is estimated to rise to 592 million (IDF Diabetes Atlas Sixth Edition, 2013). Given the growing prevalence of type 2 diabetes in all countries, diabetic macular oedema (DME), which more frequently occurs in this subtype of the disease, is dramatically on the rise and is currently the leading cause of vision loss in patients with diabetes (Ding & Wong 2012; Mathew et al. 2015). Data collated from 22 896 individuals with diabetes from 35 studies in the USA, Australia, Europe and Asia by Yau et al. (2012) showed a prevalence of 6.81% for DME. In a study carried out in the USA by Varma et al. (2014), a cross-sectional analysis of 1038 individuals with diabetes participating in the 2005 to 2008 National Health and Nutrition Examination Survey showed an overall weighted prevalence of 3.8% for DME, with higher rates amongst non-Hispanic blacks. In the UK, data extracted from 30 NHS trusts for a total of 47 771 eyes of 24 292 patients with diabetes showed presence of clinically significant macular oedema in 13.9% of the eyes (Keenan et al. 2013).

The incidence of DME increases with the severity and duration of diabetes and occurs as a consequence of diabetes-induced vascular inflammation within the retina, leading to blood–retinal barrier breakdown and fluid accumulation (Funatsu et al. 2009). High levels of pro-inflammatory mediators, including cytokines, chemokines, angiogenic factors and adhesion molecules, were

found in samples of vitreous fluid from patients with DME (Maier et al. 2008; Funatsu et al. 2009; Lee et al. 2012).

Due to a better understanding of the pathophysiology, the treatment strategy of DME has evolved over the past few years from laser photocoagulation to the intravitreal delivery of therapeutic agents, including anti-VEGFs and corticosteroids. With both pharmacotherapies, achieving effective, sustained concentrations within the retina while minimizing side-effects and injection burden has become a major challenge. While clinical trials have provided the basis for evidence-based guidelines on injection frequency and treatment regimens, real-life studies have highlighted a situation where irregular monitoring and undertreatment are a major cause of poor response to therapy in routine clinical practice (Mitchell 2014, personal communication). Hospital overload, logistic problems, cost and reimbursement issues make the tight schedules suggested by clinical trials often difficult to manage. A high treatment burden on patients and carers in terms of anxiety, work absence, appointment attendance and quality of life was also reported (Sivaprasad 2015, personal communication).

Intravitreal corticosteroid implants provide sustained, long-term delivery of the active drug, ensuring maximal intravitreal bioavailability and reducing the frequency of injections. Ozurdex® (Allergan, Inc., Irvine, CA, USA) is a biodegradable implant containing micronized preservative-free dexamethasone 0.7 mg, approved for the treatment of DME as well as macular oedema related to retinal vein occlusion and non-infectious posterior segment uveitis. The implant releases the active agent into the vitreous over a period of several months.

A few phase II and III studies, as well as small-scale, short-term exploratory studies and retrospective case studies, have shown the efficacy of Ozurdex® in improving visual and anatomic outcomes in patients with DME (Dugel et al. 2015). FDA approval for this indication was based on the Macular Edema: Assessment of Implantable Dexamethasone in Diabetes (MEAD) study, consisting of two randomized, multicentre, masked, sham-controlled, phase III clinical trials with identical protocols, evaluating safety and efficacy of Ozurdex® 0.7 and 0.35 mg. Ozurdex® was administered at fixed intervals not shorter than six months (Boyer et al. 2014). Although by the end of the study eyes treated with Ozurdex® significantly improved visual acuity (VA) with respect to the sham group, some fluctuation in VA was evident during the follow-up. By analysing the results of the first six months of the study, it becomes apparent that the initial visual gain in the groups treated with the Ozurdex® implant underwent a mild, steady decline between 3 and 6 months, which might be due to a progressive decrease in efficacy of the drug starting from months 3 to 5.

The aim of the our study was to evaluate whether a different treatment schedule with monthly monitoring and PRN treatment might hold advantages as compared to a fixed six-month regimen similar to the one of the MEAD study.

Materials and Methods

Study design

This was a prospective, multicentre, randomized study where patients with clinically significant DME were assigned to treatment at baseline either with a single Ozurdex® implant during the entire six-month follow-up or Ozurdex® implant followed by retreatment on an individualized basis (PRN) over the same period of time. Patients were recruited in three university centres in Italy (Udine, Bari, Sassari-UDBASA). The study protocol followed the tenets of the Declaration of Helsinki and was approved by the local institutional review board. Written, informed consent was obtained from all the participants before entering the study.

Patient selection

Patients were included in the study if they (1) were older than 18 years of age; (2) had diffuse DME, defined as clinically significant macular oedema (as classified by the ETDRS) with a generalized breakdown of the inner blood–retinal barrier and diffuse fluorescein leakage involving the foveal centre and most of the macular area on fluorescein angiography; (3) had central foveal thickness (CFT) greater than 250 μm on optical coherence tomography (OCT); and (4) had best corrected visual acuity (BCVA) between 0.2 and 1.3 logarithm of the minimum angle of resolution (logMAR).

Exclusion criteria were the following: (1) history of uncontrolled glaucoma (defined as intraocular pressure >25 mmHg despite treatment) or low-tension glaucoma, (2) history of systemic or ocular corticosteroid medication within 6 months before the baseline evaluation, (3) active intraocular inflammation or systemic infection, (4) glycosylated haemoglobin (HbA1c) rate above 10% and (5) loss of vision as a result of other causes.

Baseline assessment

All subjects underwent a complete ophthalmologic examination, including BCVA assessment on standard Early Treatment Diabetic Retinopathy Study (ETDRS) charts and standardized procedures, undilated slit-lamp biomicroscopy examination, Goldmann applanation tonometry and dilated fundus examination. Colour fundus photography and fluorescein angiography were performed (TRC 50 IX camera and acquisition software Imagenet i-base; Topcon Optical Co., Tokyo, Japan). Macular scans were obtained with a spectral domain optical coherence tomography (SD-OCT) equipment (Topcon 3D OCT-2000; Topcon Medical System, Oakland, NJ, USA and Cirrus; Carl Zeiss Meditech, Inc. Dublin, CA, USA).

Injection procedure, regimen and follow-up

At baseline, all patients received a 0.7-mg intravitreal dexamethasone implant (Ozurdex®, Allergan Inc., Irvine, CA, USA), injected at the pars plana, 3.5–4 mm from the surgical limbus in the inferotemporal quadrant, using the proprietary applicator. The injection procedure was performed under sterile conditions and using topical anaesthesia by an experienced retinal physician. Povidone–iodine 5% eyedrops were instilled 2 min before the injection, followed by topical antibiotics at the end of the procedure and four times daily for the following 7 days.

The patients were assigned to two groups. In the first group (PRN group), patients were treated on as-needed basis: following the initial intravitreal dexamethasone implant, they were assigned to a PRN treatment schedule

with monthly monitoring visits. Retreatments were performed in presence of an increment of 0.1 LogMAR or more from the best previous score and/or an increase in central retinal thickness of 50 μm or more compared with the lowest previous value.

In the second group (fixed-regimen group), patients were treated according to the MEAD protocol: they received only one injection of dexamethasone at baseline and were scheduled for monthly follow-up examinations. The study duration was 6 months for all patients.

Efficacy and safety assessment

The primary efficacy outcome was change in BCVA (logMAR). Secondary outcomes included reduction in central retinal thickness (CRT) and the number of injections administered. At every monthly follow-up visit, all patients received a complete ophthalmic assessment and OCT evaluation. Safety was assessed by recording the incidence of ocular and non-ocular adverse events and IOP changes. All patients were followed-up for potential side-effects secondary either to the surgical procedure or to the steroid treatment. Intraocular pressure and HbA1c rate were also monitored during the follow-up.

Statistical analysis

Statistical analyses were carried out using repeated-measure ANOVAS with Greenhouse–Geisser correction and a significance level of 5% followed by a Dunnett's multiple comparison *post hoc* test. Between-group comparison was performed using Student's *t*-test. The Fisher's exact test was used for categorical variables.

Results

Baseline patient characteristics

Forty-two eyes of 38 patients fulfilled the inclusion criteria and were included in the study. Twenty eyes were assigned to the PRN group and 22 to the fixed-regimen group. Baseline characteristics were similar in both cohorts (Table 1). Mean age was 66 ± 11 years. Mean BCVA was 0.6 ± 0.3 LogMAR (20/80 Snellen) in both groups. Mean CRT was 482 ± 156 μm in the PRN group and 544 ± 149 μm in the fixed-regimen group. Duration of DME was approximately 2 years in both groups.

Five eyes (25%) in the PRN group and eight eyes (36%) in the fixed-regimen group were treatment naïve. Non-responders to anti-VEGF therapy were 55% (11 eyes) in the first group and 41% (9 eyes) in the second group. Previous anti-VEGF treatment had been administered monthly for the first 3 months and PRN subsequently. The mean number of anti-VEGF injections in the 6 months prior to entering the study was 4.4 ± 1.2 and 5 ± 1.7 in the PRN and fixed-regimen groups, respectively. While none of the patients in the fixed-regimen group had been treated with steroids before, six eyes in the PRN group had received intravitreal triamcinolone injections in the 6 months prior to the study. In both groups, 35% (PRN) to 41% (fixed-regimen) of patients had received macular laser in the past.

Efficacy assessment

Best-corrected visual acuity (BCVA) changes over the 6 months of the study in the two groups can be seen in Fig. 1. Following an equally steady, initial gain up to month 1, and maintenance up to month 3, vision started to decline in the fixed-regimen group. At 6 months, a difference of 0.11 logMAR in BCVA could be observed between the two groups. Although this difference was not statistically significant, a trend towards maintenance versus decline of vision diversified the outcomes. Figure 2 represents the morphological changes in terms of CRT. In both groups, significant reduction in CRT was achieved up to month 2, when the fixed-regimen group had begun to revert to pretreatment level. At 4 and 5 months, the difference in thickness between the two groups was statistically significant ($p = 0.001$ at month 4 and $p = 0.012$ at month 5).

Anti-VEGF resistant eyes included in the PRN group experienced a mean BCVA gain of 0.17, 0.14, 0.16, 0.11, 0.11, 0.10 logMAR after 1, 2, 3, 4, 5 and 6 months of follow-up. Similarly, CRT decreased ($p < 0.01$) by 174, 184, 205, 183, 148 and 152 μm at the same time-points. In the fixed group, anti-VEGF unresponsive eyes improved by 0.18, 0.15, 0.17, 0.16, 0.07, 0.02 logMAR 1, 2, 3, 4, 5 and 6 after treatment. In the same eyes, CRT decreased ($p = 0.03$) by 184, 180, 120, 105, 78 and 52 μm at the same time-points. In the fixed group, eyes showing a ≥ 50 μm increase in CRT compared to lowest previous value were 2 at month 3, 4 at month 4, 8 at month 5 and 11 at month 6. Functional and

Table 1. Baseline characteristics.

	PRN group	Fixed group	p-value
All eyes, *n*	20	22	
Female gender, *n* (%)	4 (20%)	10 (45%)	0.1
Age, mean ± SD, (median;range) years	70 ± 9.6 (70;48–80)	65 ± 13.3 (68;33–86)	0.1
DME duration, mean ± SD, (median;range) months	21 ± 20 (12;1–72)	23 ± 16 (17;2–60)	0.8
Phakic eyes, *n* (%)	15 (75%)	17 (77%)	0.9
Best-corrected visual acuity, (mean ± SD), (median;range) logMAR	0.6 ± 0.3 (0.5;1.3–0.1)	0.6 ± 0.3 (0.6;1.2–0.2)	0.9
Median best-corrected visual acuity, (Snellen equivalent);range	20/80; 20/400–20/25	20/80; 20/320–20/32	
Central retinal thickness, (mean ± SD), μm (median;range)	482 ± 156 (458;301–879)	544 ± 149 (511;369–789)	0.2
Previous ocular treatment			
None, *n* (%)	6 (30%)	11 (50%)	0.2
Anti-VEGFs, *n* (%)	11 (55%)	9 (41%)	0.16
Intravitreal steroids, *n* (%)	6 (30%)	0 (0%)	0.01
Macular laser, *n* (%)	7 (35%)	9 (41%)	0.23

DME = diabetic macular oedema; logMAR = logarithm of minimum angle of resolution; *n* = number; PRN = pro re nata; SD = standard deviation; VEGF = vascular endothelial growth factor.

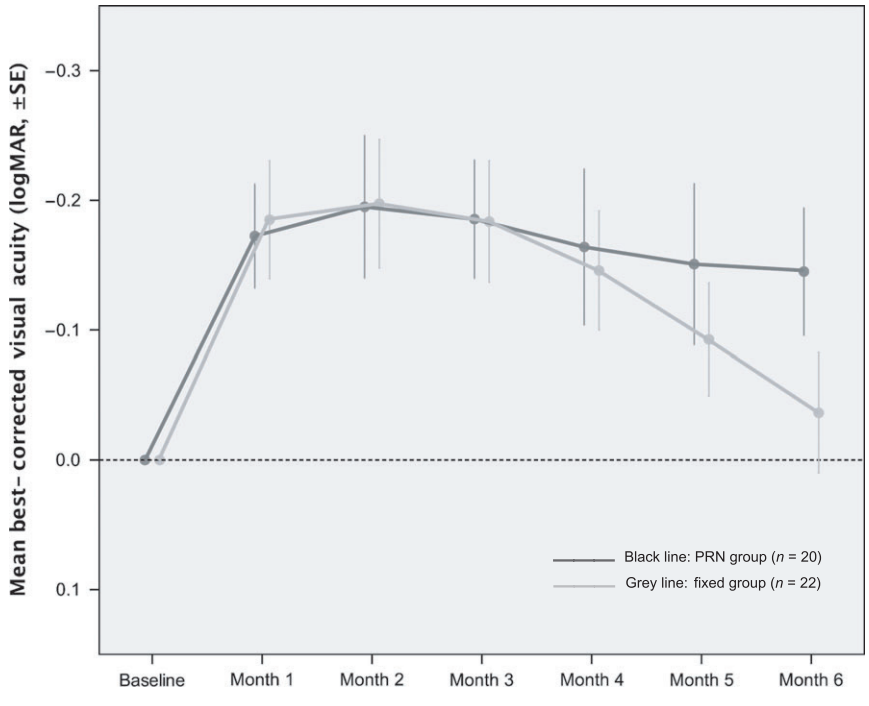

Fig. 1. Best-corrected visual acuity changes during 6 months of follow-up in patients treated on as-needed basis ($N = 20$; PRN group, presented as black line) and treated with a single dexamethasone injection ($N = 22$) (fixed-regimen group, presented as grey line).

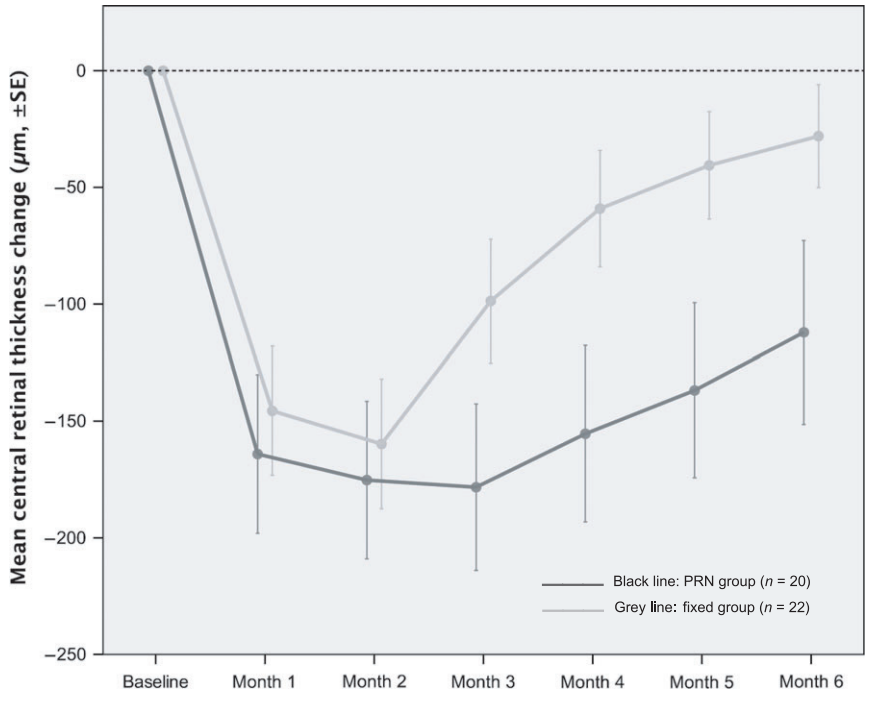

Fig. 2. Central retinal thickness changes during 6 months of follow-up in patients treated on as-needed basis ($N = 20$; PRN group, presented as black line) and treated with a single dexamethasone injection ($N = 22$; fixed-regimen group, presented as grey line).

morphological outcomes in pseudophakic eyes are reported in Table 2.

Of the 20 eyes in the PRN group, eight (40%) required no further treatment during the 6 months of the study. Three eyes (15%) were retreated at 4 months, six (30%) at 5 months and three (15%) at 6 months. Overall, the mean number of injections performed in the PRN group was 1.6 in 6 months.

Safety assessment

Increased intraocular pressure (IOP) requiring pharmacological therapy was found in a higher percentage of eyes in the PRN group (30%, six eyes, versus 14%, three eyes) ($p = 0.13$). IOP elevation was recorded at month 1 (two eyes) and month 2 (one eye) in the fixed group and at month 1 (three eyes), month 2 (two eyes) and month 5 (one eye – 1 month after a second treatment) in the PRN group. In all cases, IOP elevation resolved with topical medications within 1 month, with no effects on visual acuity. Cataract surgery was needed in six (40%) of the 15 phakic eyes of the PRN group and eight (47%) of the 17 phakic eyes of the fixed-regimen group. The difference was not statistically significative ($p = 0.26$). No systemic adverse events were registered.

Discussion

This study shows that a personalized treatment schedule with monthly monitoring and retreatment as needed is effective in maintaining for up to 6 months the functional and anatomical benefits of Ozurdex®.

In pharmacokinetic studies in non-human primates, dexamethasone from the intravitreal implant was detected in the retina and vitreous humour for 6 months. However, peak concentrations were achieved in the first 2 months, followed by rapid decrease between days 60 and 90. In the following months, the drug was shown to maintain very low concentrations, falling below the limit of quantification at month 6 (Lee et al. 2010; Chang-Lin et al. 2011). An analogous pharmacokinetic behaviour of the implant in the human eye may account for the decreased clinical benefits in terms of mean visual acuity and CRT from the third months postinjection, as shown in the MEAD trial. The MEAD trial involved 131 sites in 22 countries and enrolled a total of 1048 patients, of which approximately 60% completed the study. Patients were eligible for retreatment with the Ozurdex® implant only after a minimum of 6 months from the previous study treatment and in presence of residual oedema. Compared with the sham group, patients treated with Ozurdex® experienced a rapid and significant visual acuity improvement. Reduction in the overall

Table 2. Functional and morphological outcomes in pseudophakic eyes.

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Pseudophakic eyes at the baseline in PRN group (n = 5)						
BCVA change, mean ± SD, (median) logMAR	−0.2 ± 0.2 (−0.1)	−0.1 ± 0.1 (−0.1)	−0.2 ± 0.1 (−0.2)	−0.2 ± 0.2 (−0.1)	−0.1 ± 0.2 (0)	−0.1 ± 0.2 (−0.1)
CRT change, mean ± SD, μm	−275 ± 151	−280 ± 156	−271 ± 186	−249 ± 202	−194 ± 222	−172 ± 198
Pseudophakic eyes at the baseline in fixed group (n = 5)						
BCVA change, mean ± SD, (median) logMAR	−0.2 ± 0.2 (0)	−0.2 ± 0.2 (−0.1)	−0.1 ± 0.2 (−0.1)	−0.1 ± 0.2 (0)	−0.05 ± 0.2 (0)	−0.05 ± 0.2 (0)
CRT change, mean ± SD, μm	−167 ± 131	−181 ± 137	−119 ± 155	−57 ± 76	−43 ± 73	−19 ± 68

LogMAR = logarithm of minimum angle of resolution; n = number; PRN = pro re nata; SD = standard deviation; BCVA = best-corrected visual acuity; CRT = central retinal thickness.

visual benefit from the treatment during the second year was related to the onset of cataract in some of the patients, but anatomic results in terms of reduced CRT remained stable despite the vision loss in those eyes. In a subset of pseudophakic eyes, the visual acuity benefit remained stable over the 3 years of the study. By the end of the study, treatment with Ozurdex® resulted in clinically meaningful improvement in BCVA independent of the lens status at baseline.

However, when paying close attention to the visual acuity responses, it becomes evident that the drug's effect declined between month 3 and month 6. This suggests that a relevant proportion of DME patients may require a more frequent treatment.

In our study, a similar behaviour was seen in the fixed group, which showed a mild reduction in visual gains starting at month 4. On the opposite, patients treated with a PRN regimen showed a stable visual acuity improvement. These results were also mirrored by morphological findings as evaluated with OCT. These results are independent from lens status at baseline.

With regard to CRT response to treatment, it must be noted that curves tend to diverge as early as at month 3. This is may be due to the fact that two patients in the fixed group showed a recurrence of DME at month 3, whereas in the PRN group, the earliest recurrence was recorded at month 4. However, this discrepancy may be attributed to the relatively small sample size and a consequent random error attributable to chance.

Also, the baseline unbalance in previously steroid-treated eyes in the two groups may have influenced the outcome in CRT.

A *post hoc* subgroup analysis was performed for patients who were classified as anti-VEGF non-responders by the investigators. Ozurdex® implant showed a notable and fast effect in both visual acuity amelioration and CRT reduction. Patients in the PRN group maintained the initial gain throughout the study, while patients in the fixed group started to lose the functional and morphological benefit from month 4.

In view of a potentially more frequent administration of Ozurdex® in some cases, as required by a PRN regimen, the benefits of corticosteroid therapy have to be balanced against the risk of IOP elevation and cataract formation. Of the three corticosteroids used intravitreally, dexamethasone has the highest safety profile. Compared to fluocinolone and triamcinolone acetonide, it is less lipophilic and therefore accumulates in a lesser quantity in the trabecular meshwork and in the lens (Thakur et al. 2011). In clinical studies, the dexamethasone implant has been associated with a significantly lower incidence of IOP elevation and cataract compared to the fluocinolone implant or intravitreal triamcinolone acetonide (Boyer et al. 2014).

In our study, more frequent administration of dexamethasone in the PRN group was associated with a higher, but not statistically significant, rate of IOP increase requiring pharmacological therapy although this difference was not statistically significant. However, in all cases, this side-effect was manageable with topical medications. Cataract rate did not differ significantly between the two groups.

Conclusion

Our results suggest that individualized treatment with close monitoring produces durable responses with an acceptable safety profile. Moreover, Ozurdex® showed a valuable functional and morphological benefit on eyes resistant to anti-VEGF treatment.

The small sample size is a limitation of our study and larger clinical trials with a longer follow-up are needed to assess the safety and efficacy of a PRN regimen in DME patients.

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