Dexamethasone implant improves anatomic response to anti-VEGF therapy in treatment-resistant Polypoidal Choroidal Vasculopathy

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Research Article

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Abstract

Background: A significant proportion of eyes with polypoidal choroidal vasculopathy (PCV) can be resistant to anti-vascular endothelial growth factor (VEGF) injections. We evaluated the efficacy of combination of Dexamethasone intravitreal implant (DXI) and anti-VEGF therapy in eyes resistant to anti-VEGF monotherapy.

Materials and Methods: In this retrospective study, polypoidal choroidal vasculopathy (PCV) resistant to anti-VEGF injections were additionally injected with a Dexamethasone implant along with an anti-VEGF agent. Best-corrected visual acuity (BCVA), slit lamp examination, intraocular pressure, fundus evaluation and optical coherence tomography (OCT) data were analyzed. Anatomical response on OCT was the primary outcome measure. Gain in visual acuity, and injection-free interval after the Dexamethasone implant were evaluated as secondary outcome measures.

Results: Twelve eyes of 11 patients were included in the study. The mean age of patients was 70.2 ± 11.8 years, and there were 8 females. The mean follow-up duration after DXI was 24.5 ±11 months. The mean number of anti-VEGF injections before DXI was 4.2 ± 1.9. The mean injection-free interval in these patients after DXI was 4.7± 0.6 months, which was significantly greater than the pre-injection mean of 1.6 ± 0.4 months ($p<0.001$). The median log MAR BCVA immediately prior to DXI was 0.41 (Interquartile Range IQR 0.30-1.02) and after injection was 0.60 (IQR 0.27-1.03), which was not significant ($p=0.59$). The median OCT thickness after DXI in was 305 microns (IQR 206-417), which was significantly less than the pre-injection OCT thickness of 547 microns (IQR 432-685) ($p=0.005$). The mean IOP before DXI was 14.7 ± 2.3 mm Hg, and after the injection was 14.3 ± 2.7 mm Hg ($p=0.36$).

Conclusions: Dexamethasone implant combined with anti-VEGF treatment can prolong the treatment-free interval in eyes with PCV resistant to anti-VEGF injection, while maintaining visual acuity.

Introduction

Intravitreal injection of anti-vascular endothelial growth factor (VEGF) is the standard of care for choroidal neovascular membrane (CNVM) due to neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV).[1-4] However, a significant portion of eyes treated with anti-VEGF show little or no response to the therapy.[5,6] Estimates of the prevalence of this anti-VEGF resistance among eyes with CNVM vary significantly in the literature based on anti-VEGF drug of choice, specific sub-type diagnosis such as nAMD or PCV, treatment style (prn vs treat-and-extend vs monthly regimen) and the ethnic population.[6-9]

Various inflammatory cytokines, such as macrophage derived chemokine (MDC), interleukins, and monocyte chemotactic protein levels were significantly higher in PCV patients have been shown to be elevated in eyes with PCV.[10] Pharmacologic therapies which reduce inflammation in the eye may improve the outcomes in eyes with PCV. Dexamethasone implant (Ozurdex (DXI); Allergan, Irvine,

California, USA), combined with anti-VEGF therapy, could improve the response to anti-VEGF agents in treatment-resistant PCV. A study by Kuppermann et al combining DXI with anti-VEGF agents in patients with nAMD demonstrated that the injection-free interval in patients receiving DXI along with anti-VEGF therapy was significantly longer than in patients receiving placebo with anti-VEGF therapy.[11] However, the LuceDex trial did not show any difference in the number of injections between combination therapy and anti-VEGF monotherapy, although there was more visual gain in the combination therapy arm.[12] A few other studies have evaluated the efficacy of a combination treatment of DXI and anti-VEGF in nAMD patients resistant to anti-VEGF, but with contrasting outcomes.[13-15] None of these patients included PCV. The purpose of this study was to evaluate visual outcomes and retreatment intervals after combination of Dexamethasone intravitreal implant (DXI) and anti-VEGF therapy in eyes resistant to anti-VEGF therapy in PCV.

Methods

The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the local Institutional Review Board. All study participants gave a written informed consent before enrollment. Patients were recruited from April 2017 through August 2019.

Patient eligibility

Inclusion criteria:

Key eligibility criteria included: (1) CNVM due to PCV; (2) minimum of 3 consecutive monthly anti-VEGF injections in the previous 12 weeks with ≤10% reduction in central sub-field thickness;

Exclusion criteria:

Key exclusion criteria included: (1) decrease in visual acuity due to causes other than PCV; (2) presence of glaucoma or steroid response; (3) use of intraocular or periocular corticosteroids in the study eye within the previous 6 months; (4) previous vitreoretinal surgery in the study eye or anticipated surgery within 12 months of enrollment.

Eyes were injected with 1) intravitreal dexamethasone implant (Ozurdex, Allergan, Irvine, CA, USA) and (2) 1.25 mg bevacizumab, 0.5 mg ranibizumab, or 1.25 mg ziv-aflibercept. Patients were evaluated again every month. Patients were re-injected with intravitreal anti-VEGF if there was persistent intravitreal or subretinal fluid at any visit.

Ocular Evaluation

All participants had a comprehensive ocular examination including best-corrected visual acuity (BCVA) testing, dilated fundus examination with slit-lamp biomicroscopy, color fundus photography, fundus fluorescein (FFA) and indocyanine green angiography (ICGA, Heidelberg Engineering GmbH, Heidelberg, Germany) and OCT (Triton DRI, Topcon, Japan). Patients underwent OCT at subsequent visits.

Intravitreal injections

Intravitreal injections were administered using a strict aseptic technique under topical anesthesia in an outpatient procedure room. Intravitreal injections were performed with 29-gauge needle inserted through the inferotemporal pars plana, 4 mm posterior to the limbus in phakic eyes and 3.5 mm in pseudophakic eyes. In eyes receiving combination treatment, DXI was injected after the anti-VEGF injection in the same sitting.

Outcome measures

Since this study was performed in resistant PCV, anatomical response on OCT was the primary outcome measure. Gain in visual acuity and injection-free interval after the dexamethasone implant were evaluated as secondary outcome measures.

Statistical Analysis

Data were analyzed using STATA version 16.1 (College Station, Texas, USA). The continuous data were checked for the normality of distribution by Shapiro-Wilk test and described in mean ± standard deviation if normally distributed and median with inter-quartile range (IQR) if otherwise. Pre-and post-injection BCVA and OCT thickness were compared by Wilcoxon signed-rank test, while IOP was compared by Paired t-test. Categorical data were described in proportions and compared pre- and post-injection by McNemar test. Relationships between continuous data were assessed by Spearman correlation. Kaplan-Meier survival analysis was used to estimate the probability of first injection after DXI. A p-value of <0.05 was considered statistically significant.

Results

Twelve eyes of 11 patients were included in the study. The mean age of patients was 70.2 ± 11.8 years, and there were 8 females. The mean follow-up duration after DXI was 24.5 ± 11 months (Table 1). All eyes with PCV were confirmed by ICGA. The mean number of anti-VEGF injections before implant was 4.2 ± 1.9. All eyes received an injection along with DXI; bevacizumab in 2 eyes, ranibizumab in 4 eyes, and ziv-aflibercept in 6 eyes.

Table 1
Demographic data of patients with PCV

Characteristics	n (%)
Mean age (years)	70.2
Male	4 (33.3%)
Female	8 (66.6%)
Right eye (OD)	5 (41.6%)
Left eye (OS)	7 (58.3%)
Mean prior Anti-VEGFs (n)	4.2 ± 1.9

Visual acuity

The median BCVA before DXI injection was 0.41 (IQR,0.30–1.02), and 1 month after the injection was 0.40 (IQR, 0.30–1.05; p = 0.75). At the last visit, there was no significant change (p = 0.59) in BCVA with a median of 0.60 (IQR, 0.27–1.03). (Fig. 1)

Retinal thickness

The median OCT thickness before injection was 547 microns (IQR, 432–685), which decreased to 305 microns (IQR, 206–417) with a significant value (p = 0.005). The median change in OCT thickness was 207 microns (IQR, 30–559). (Fig. 2) There was a significant (p = 0.004; r_s = 0.74) positive correlation between pre-injection OCT thickness and change in OCT thickness in eyes with PCV.

Retinal fluid compartments

The proportion of eyes with PCV having pigment epithelial detachment (PED) before injection was 76.9%, which reduced to 53.8% and 30.8% after 1st month and final follow-up respectively. At the last visit, the proportion of eyes with PED was 7.7% and a statistical significance (p = 0.03) was noted in the reduction of PED in eyes with PCV. The proportion of eyes having intra-retinal fluid and sub-retinal fluid was also reduced at the last visit which was significant (p = 0.01). (Fig. 3)

Figures 4 and 5 show representative OCT images from two patients who initially showed no response to anti-VEGF monotherapy, yet showed good response and reduction in CRT after combination treatment with DXI and anti-VEGF. Ozurdex was not repeated in any patient, as this was a pilot study.

The mean injection-free interval in these patients after DXI was 4.7 ± 0.6 months, which was significantly greater than the pre-injection mean of 1.6 ± 0.4 months (p < 0.001). The injection-free interval was not correlated with number of injections (p = 0.23) and pre-injection OCT thickness (p = 0.56). The survival

analysis estimates of first injection after DXI were 20% at 3 months, 65% at 6 months, and 75.6% at 12 months. (Fig. 6)

Discussion

Intravitreal steroid injections in resistant nAMD have been studied with variable results.[13–19] Inflammation is known to play a key role in the pathogenesis of PCV and nAMD.[10, 20] Oxidative stress has been shown to initiate the assembly of inflammasome complexes in the Retinal Pigment Epithelium.[21] Complement components C3a and C5a have been shown to promote CNVM.[22, 23] Corticosteroids counteract macrophages and related cytokines involved in inflammation and neovascularization.[24, 25] There is also evidence that combination of intravitreal corticosteroids and anti-VEGF agents can decrease tachyphylaxis, or the decline in potency of these medications after a number of injections.[26]

Though intravitreal dexamethasone could have substantial impact, it is cleared from the eye quickly, with a half-life of less than 3.5 hours.[27] In contrast, the Dexamethasone intravitreal implant used in this study has biological activity in the eye for 4–6 months.[28] A small retrospective study on anti-VEGF resistant eyes also found that CRT declined significantly, which was held up until 3 months post-implantation.[13] This study also reported a total absence of any fluid 3 months after dexamethasone injection in 71.4% of their patients.

The stability of BCVA after DXI in these anti-VEGF resistant PCV patients in our study is understandable, given the fact that DXI was given after anti-VEGF therapy had been started. It is possible that the usual decline in BCVA for these patients associated with the normal course of PCV on anti-VEGF therapy has been slowed by DXI. If this is the case, vision stabilization in these patients with a reduced burden of injections would indeed be a desirable outcome.

Given that the frequency of anti-VEGF injections poses a huge burden on patients, reducing the burden of injections by increasing the time between injections, must be a goal of future therapy.[29] However, for the significant portion of patients who fail to respond to anti-VEGF therapy, combination with steroids could potentially have a role in reducing the resistance to anti-VEGF therapy. Our study in eyes with PCV demonstrates that the burden of frequent injections can be reduced with the addition of a steroid extended-release implant by significantly increasing the injection-free interval to more than 4 months. This is a substantially longer duration compared to other studies in nAMD, and promises to reduce the treatment burden significantly. Our study shows that intravitreal steroid implants can also lead to significant reduction of macular edema. In all but two patients in this study, Central Retinal Thickness (CRT) declined during the month after the implant was placed. Significantly fewer patients had any fluid in any compartment on OCT after the implant.

The limitations of our study include the relatively small sample size, as well as the fact that it was a retrospective study. A larger, randomized, prospective study of PCV would be more clearly able to evaluate the effects of the DXI implant used in combination with anti-VEGF therapy, as well as determine what

biomarkers or trends are unique to patients who still fail to respond significantly to this dual therapy. Our small sample could not evaluate the impact of high reflective dots in the choroid or the retina. Strengths of our study include significant increase of the injection-free interval after steroid implant in resistant cases. There were no significant safety concerns in this small study,

Conclusion

This study shows that the addition of intravitreal dexamethasone implant in PCV, resistant to anti-VEGF, could stabilize visual acuity and partially restore foveal anatomy. Further studies with larger sample sizes, should also look into biomarkers of eyes resistant to anti-VEGF,

List Of Abbreviations

BCVA	Best Corrected Visual Acuity
CNVM	Choroidal Neovascular Membrane
CRT	Central Retinal Thickness
DXI	Dexamethasone Implant
FFA	Fundus Fluorescein Angiography
ICGA	Indocyanine Green Angiography
IOP	Intraocular Pressure
IQR	Interquartile Range
ME	Macular Edema
nAMD	Neovascular Age Related Macular Degeneration
PCV	Polypoidal Choroidal Vasculopathy
PED	Pigment Epithelial Detachment
OCT	Optical Coherence Tomography
VEGF	Vascular Endothelial Growth Factor

Declarations

Ethics approval and consent to participate

A written consent was obtained from patients in accordance with the declaration of Helsinki. The study was approved by respective Ethics Committees.

Consent for publication

Not Applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on request.

Competing interests

None of the authors have any competing interests.

Funding

None

Authors' contribution

RN, KM contributed to data collection, analysis and interpretation data, preparation of the manuscript and provided major revisions to the manuscript. RR, AM, MPS, RA and SP contributed to interpretation and final analysis of manuscript. AM and KM performed statistical analysis. All authors participated in the development and writing of the manuscript and approved the final article for publication.

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Tables

Table 1: Demographic data of patients with PCV

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Figures

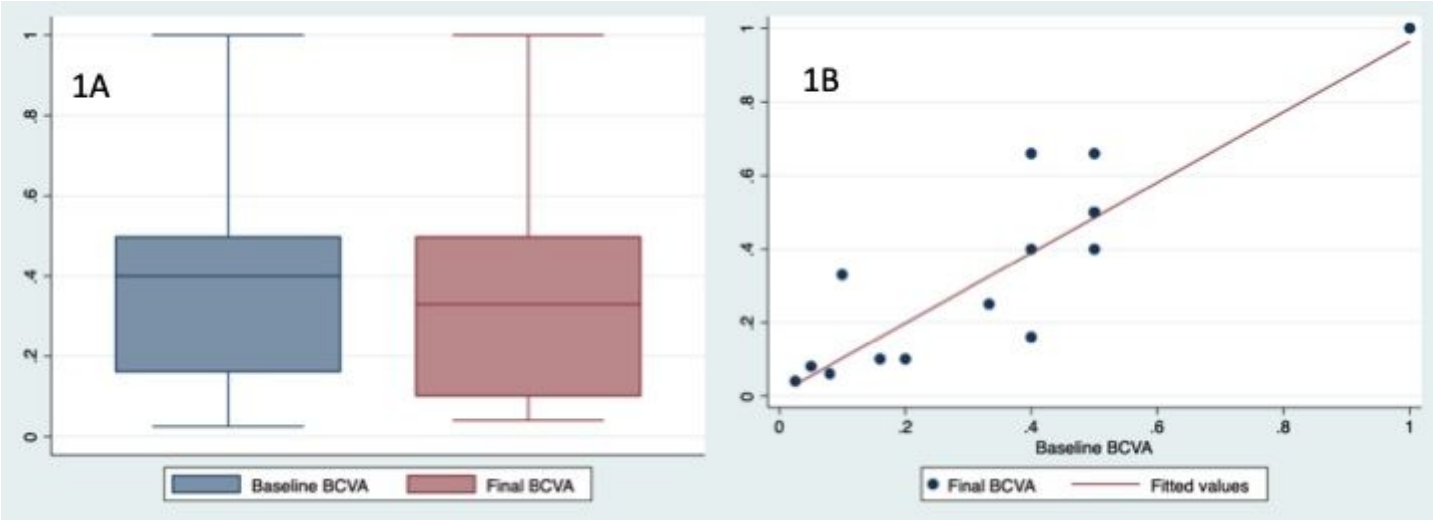

Figure 1

1A. Box plot comparison of Best-Corrected Visual Acuity (BCVA) expressed as a decimal before DXI (left) and at last follow up after DXI implantation (right). BCVA was maintained during this interval. 1B. Scatter plot showing that the final BCVA was correlated with baseline BCVA.

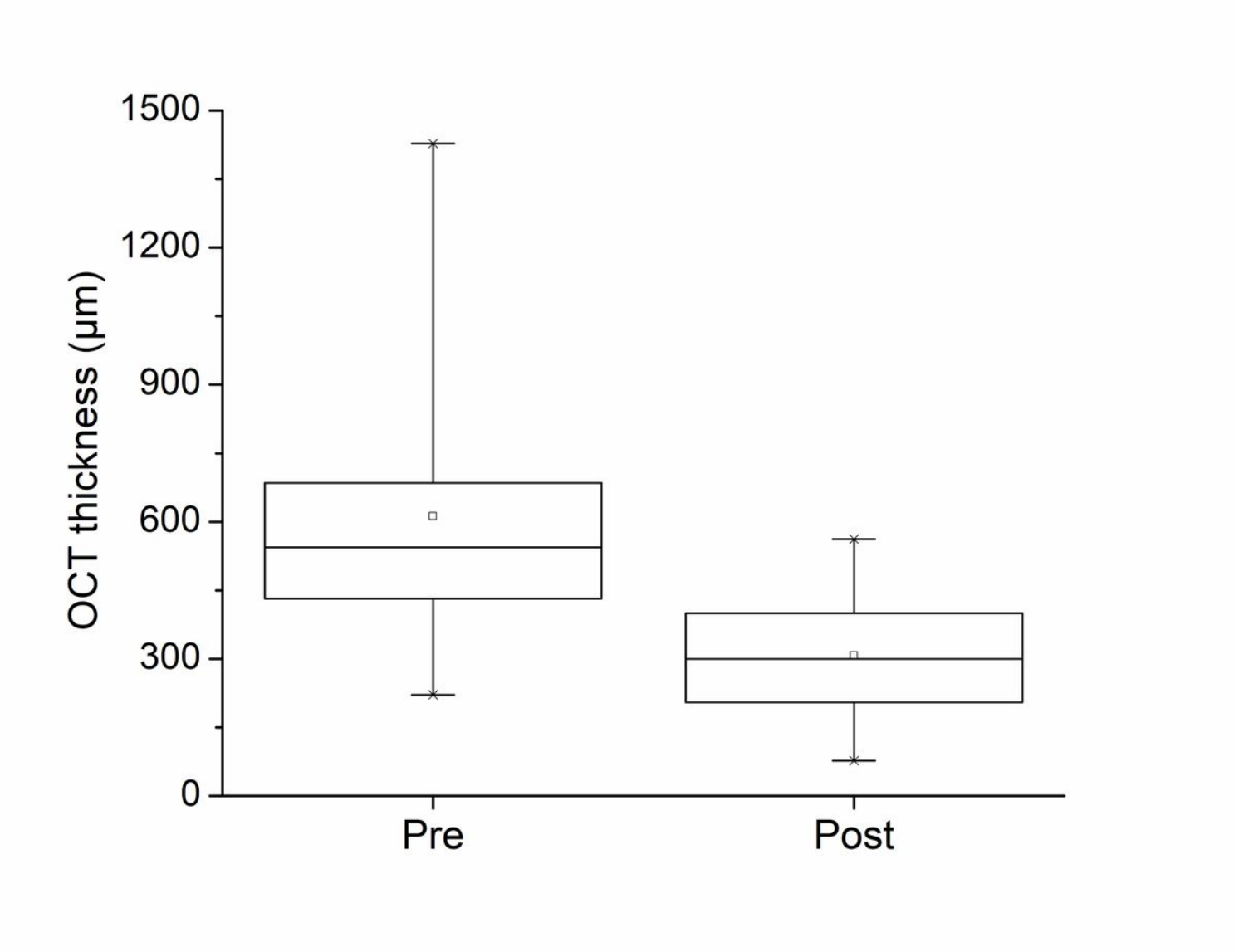

Figure 2

Box plot comparing Central Retinal Thickness (CRT) before DXI (left) and after DXI (right). There was a significant reduction in central retinal thickness before and after DXI implant.

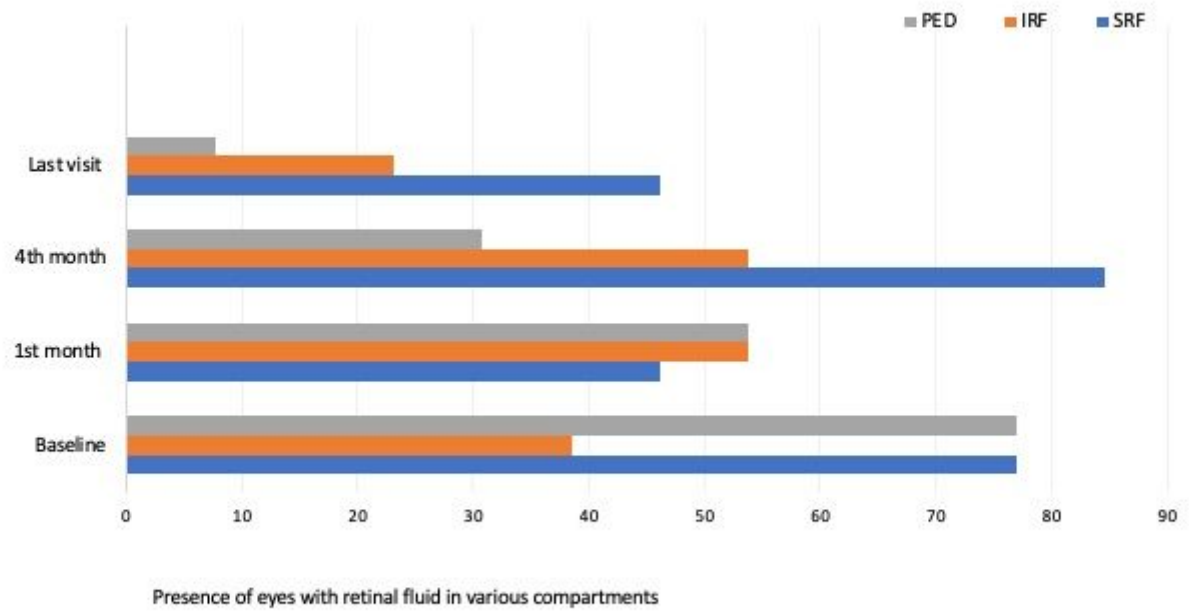

Figure 3

Presence of retinal fluid in various compartments at baseline and after injection. There was a significant reduction in fluid in all compartments. IRF: intraretinal fluid SRF: subretinal fluid PED: pigment epithelial detachment

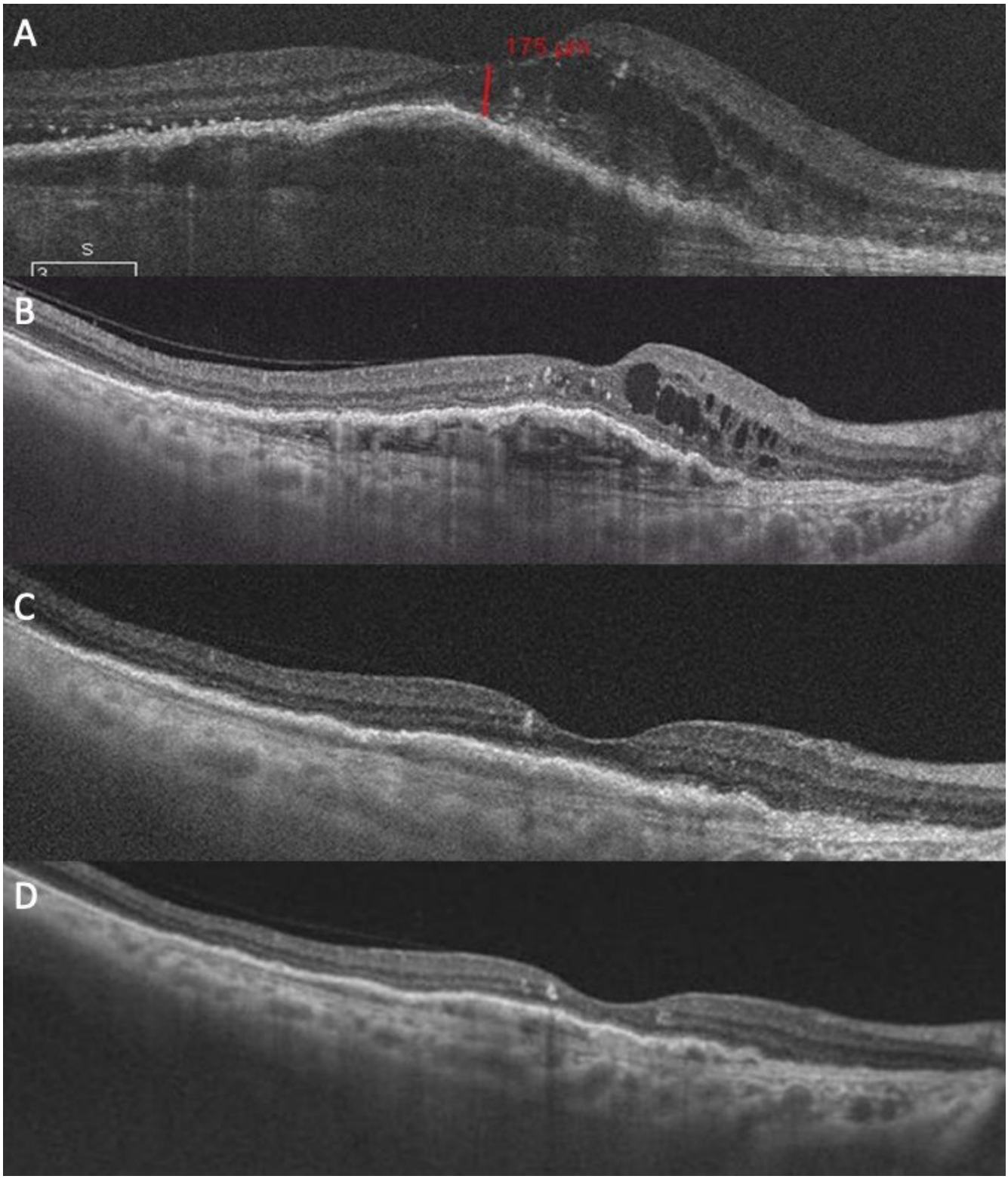

Figure 4

The patient had received two monthly ranibizumab injections with no response (3a and 3b show OCT images after each injection). Figure 3c and 3d are OCT images taken after the combination of ranibizumab and DXI injections, which showed good response with no intra-retinal or sub-retinal fluid three weeks and two months after the injection, respectively.

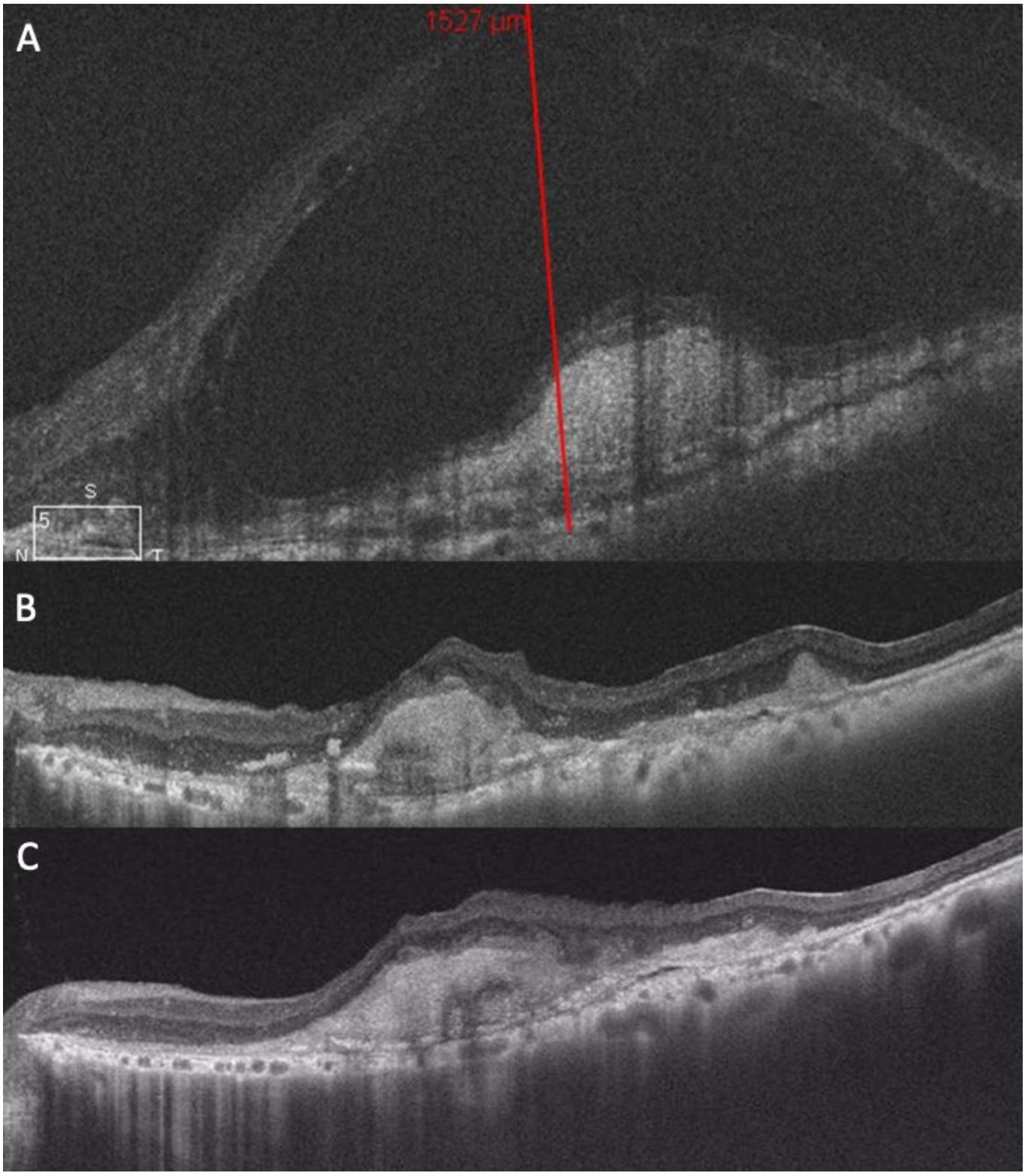

Figure 5

The patient had received four bevacizumab and one ranibizumab injections with poor response. (Figure 4a shows OCT images after these injections). Figure 4b and 4c show complete resolution of macular fluid after ranibizumab and DXI implant, one and six months later, respectively.

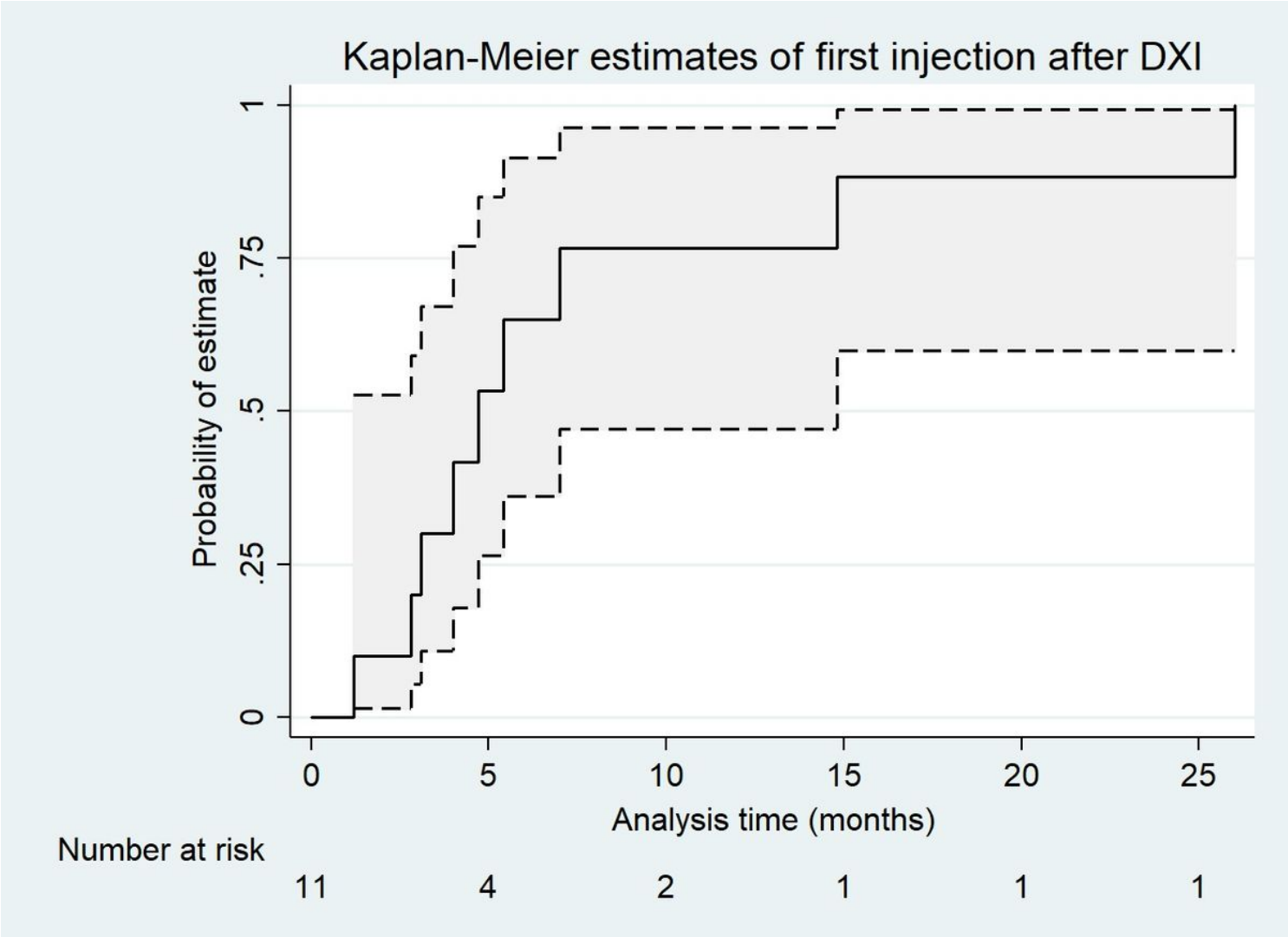

Figure 6

Kaplan Meier survival analysis estimate of risk of repeat anti-VEGF injection after DXI implant.