Short-term Outcomes of Refractory Diabetic Macular Edema Switch from Ranibizumab to Dexamethasone Implant and the Influential Factors: A Retrospective Real World Experience.

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Abstract

Background: To evaluate the effectiveness and safety of intravitreal dexamethasone (DEX) implants in refractory diabetic macular edema (DME) treated by intravitreal ranibizumab.

Methods: We retrospectively analyzed DME patients who received DEX implant treatment after being unresponsive to at least three monthly intravitreal ranibizumab injections. The main outcomes were best-corrected visual acuity (BCVA), central retinal thickness (CRT), and intraocular pressure (IOP).

Results: Twenty-nine eyes of 26 patients who had previously received an average of 8.1 ± 4.4 ranibizumab injections were included. Patients received between one and three DEX implants during 12.4 ± 7.4 months of follow-up. The mean final CRT significantly decreased from 384.4 ± 114.4 μm at baseline to 323.9 ± 77.7 μm (p = 0.0249). The mean final BCVA was 51.4 ± 21.3 letters, which was not significant compared to baseline (44.9 ± 30.2 letters, p = 0.1149). Mean IOP did not increase significantly. All patients tolerated the treatment well without serious adverse events. Higher baseline CRT and worse BCVA correlated with better therapeutic responses.

Conclusion: Switching to DEX implant is effective and safe for treating DME non-responder to intravitreal ranibizumab in real world.

Background

Diabetes mellitus is one of the most important global health issues of the 21st century. At present, there are 425 million patients with diabetes worldwide, and this number is projected to reach 629 million by the year of 2045.[1] Diabetic retinopathy, a microvascular complication of diabetes, has an estimated prevalence of 34.6% among patients with diabetes. Diabetic macular edema (DME), a manifestation of diabetic retinopathy, develops in approximately 6.8% of patients with diabetes and is a major cause of visual loss in this population.[2]

Hyperglycemia in diabetes increases oxidative stress, inflammation, and vascular dysfunction. Oxidative stress and inflammation induce the upregulation of growth factors, such as vascular endothelial growth factor (VEGF) and cytokines, which contribute to the breakdown of the blood-retinal barrier (BRB) by disrupting the integrity of retinal vascular endothelial cell tight junctions and increasing vascular permeability.[3] The ensuing fluid accumulation, in addition to the persistent presence of inflammatory factors, causes dysfunction of the inner nuclear layer and subsequent development of DME.[4]

VEGF antagonists are frequently used as intravitreal treatments for DME, as several studies reveal that patients with DME had favorable visual and anatomic responses to ranibizumab.[5–6] However, there are still patients who, after a favorable initial response to anti-VEGF agents, showed decreased responses over time and became resistant to further intravitreal injections. This may be a result of inflammatory mediators other than VEGF contributing to the persistence of DME.[7] Increasing dosages of intravitreal injections are needed to control the disease. However, this carries an increased risk of complications and poor compliance.[8]

Corticosteroids have been demonstrated to inhibit the expression of VEGF and other inflammatory factors, thus reinforcing the BRB. The biodegradable intravitreal dexamethasone (DEX) implant provides sustained release of the anti-inflammatory corticosteroid dexamethasone into the vitreous. DEX implants have been identified as an effective treatment of DME and have recently been approved by the US Food and Drug Administration (FDA).[9–11] We thus conducted this study to investigate anatomic and functional improvements of DEX implant treatment in a group of patients with DME resistant to previous ranibizumab injections.

Methods

This retrospective, non-comparative, consecutive case series study was approved by the Institutional Ethics Committee and conducted in compliance with the tenets of the Declaration of Helsinki. We retrospectively analyzed the eyes of patients with DME that, upon unresponsiveness to intravitreal ranibizumab treatment, were treated with DEX implant between August 2013 and October 2017. Informed oral and written consent was obtained from all patients. The inclusion criteria were as follows: (1) a diagnosis of DME (the presentation of choroidal neovascularization with macular edema, confirmed by fluorescein angiography and optical coherence tomography [OCT]); (2) a history of treatment with intravitreal ranibizumab, followed by increasing or persistent sub-retinal fluid or retinal edema on OCT; and (3) the presence of refractory sub-retinal fluid after at least three monthly ranibizumab injections. The criteria for treatment with DEX implant were the same as the retreatment criteria for ranibizumab regarding the presence of intraretinal or subretinal fluid.

We recorded general patient data including age, sex, laterality, medical history, glycated hemoglobin (HbA1c), best-corrected visual acuity (BCVA), central retinal thickness (CRT), intraocular pressure (IOP), and results of external ocular and slit-lamp examinations. Each patient underwent a thorough bilateral fundus examination by indirect ophthalmoscopy, fundus photography, fluorescein angiography, and spectral-domain OCT (Cirrus HD-OCT; Carl Zeiss Meditec, Inc., Dublin, CA) scans. Over the course of the treatment, patients received between one and three injections of DEX implant 0.7 mg (Ozurdex, Allergan, Inc, Irvine, CA). Before each DEX implantation, the topical antibiotic levofloxacin (Cravit, Santen Pharmaceutical Co., Osaka, Japan) was applied. Topical and subconjunctival anesthesia was achieved by 0.5% proparacaine hydrochloride (Alcaine, Alcon Pharmaceuticals, Puurs, Belgium) before surgery. Each eye was prepared in a sterile manner using 5% povidone/iodine. The DEX implant was inserted intravitreally via a pars plana puncture (3.5 mm away from the limbus). Application of levofloxacin eyedrops was prescribed four times a day for one week after the operation. Initial management with ranibizumab and the number of subsequent treatments with DEX implant were collected. All of the patients were scheduled for monthly follow-ups.

The main outcome measures include the mean change in CRT from baseline as measured by spectral-domain OCT and mean change in BCVA (approximate Early Treatment Diabetic Retinopathy Study [ETDRS] letter scores) from baseline during monthly follow-ups. Therefore, the outcome of DEX implant after ranibizumab was evaluated by analyzing changes in retinal anatomy and vision, with reference to patient characteristics and fundus findings. Safety was evaluated by recording complications and other adverse events during the follow-up period.

As for the statistical methods, SAS 9.4 was used for analysis in this study. For comparison of cross-section data, the one-way ANOVA was used for continuous data, and the Fisher's exact test was used for categorical data. For comparison of serial data, the principle of a generalized linear mixed model (GLMM) was applied using the GLIMMIX procedure in SAS.

Results

Study Population and Treatments

A total of 29 eyes of 26 patients with DME were included in this study. The study group comprised of 14 men and 12 women, and the mean age was 62.0 ± 9.1 (range 46–84) years. The mean baseline HbA1c was 7.5 ± 1.3%. Before any treatment (baseline), the mean CRT was 384.4 ± 114.4 (range 248–727) μm (Table 1). After ranibizumab treatment, patients were followed up for an average of 12.4 ± 7.4 months. Prior to receiving DEX implant treatment, all patients had been treated with an average of 8.1 ± 4.4 (range 3–18) injections of intravitreal ranibizumab. Each eye received an average of 1.3 ± 0.6 DEX implant (range 1–3) injections.

Table 1
Baseline Characteristics of the Patients

Baseline Characteristics	mean ± SD or (%)
Age (years)	62.0 ± 9.1
Gender (n = 26)	
Female	12 (46.2%)
Male	14 (53.8%)
Eyes (n = 29)	
OD	16 (55.2%)
OS	13 (44.8%)
Baseline BCVA (letter score)	44.9 ± 30.2
Baseline CRT (μm)	384.4 ± 114.4
Baseline IOP (mmHg)	14.9 ± 3.1
Lens Status	
Phakic	20 (69%)
Pseudophakic	9 (31%)
Follow-up (months)	
Total	19.8 ± 9.0
Before Ozurdex (anti-VEGF use)	12.4 ± 7.4
After Ozurdex	7.4 ± 4.6
BCVA: best-corrected visual acuity; CRT: central retina thickness;	
IOP: intraocular pressure; VEGF: vascular endothelial growth factor.	

Anatomic Changes

All eyes showed anatomic improvement after switching to intravitreal DEX implant treatment, with significant postoperative changes in CRT as measured by OCT. After DEX implant treatment, the mean final CRT (323.9 ± 77.7, range 201–488 μm) was significantly lower than the baseline value (384.5 ± 114.4, range 248–727 μm) ($p = 0.0249$), and also significantly lower than the mean CRT at one month after the last injection of ranibizumab (375.5 ± 111.0, range 261–757 μm) ($p = 0.0265$) (Fig. 1A). The mean best CRT (the lowest CRT value recorded during follow-up)after ranibizumab treatment (302.1 ± 73.5, range 195–568 μm) was significantly lower than the baseline value ($p = 0.0004$), and it was maintained if not further improved after DEX implants (286.1 ± 56.3, range 172–414 μm) ($p < 0.0001$ compared to baseline) (Fig. 1B).

Changes in Best-Corrected Visual Acuity

After DEX implant treatment, the mean final BCVA (51.4 ± 21.3 letters) did not significantly improve as compared to baseline (44.9 ± 30.2 letters) ($p = 0.1149$) (Fig. 2A). However, the mean maximal BCVA (the highest letter score recorded during follow-up) after DEX implant (61.2 ± 17.4 letters) was significantly higher than baseline ($p = 0.0022$) (Fig. 2B).

Predictors of Therapeutic Response

Several baseline patient parameters were analyzed to explore the correlation with the treatment responses (Table 2). Thicker baseline CRT (Fig. 3), lower HbA1c, and worse BCVA (Fig. 4) had better responses to the treatment. Multivariate logistic regression and general linear model analyses confirmed the same results that thicker baseline CRT and worse baseline BCVA had better responses to the treatment.

Table 2
Clinical Parameters of Patients with Different Therapeutic Responses

	ΔCRT ≤ -50 n = 12 (41.38%)	ΔCRT > -50 n = 17 (58.62%)	*p*	ΔBCVA ≥ 15 n = 8 (27.59%)	ΔBCVA< 15 n = 21 (72.41%)	*p*
Initial CRT 2	477.17 ± 106.90	319.00 ± 63.61	< 0.0001*	420.38 ± 134.10	370.76 ± 106.37	0.305
Initial HbA1c	6.65 ± 0.59	7.99 ± 1.61	0.018*	7.12 ± 1.41	7.60 ± 1.50	0.487
Age	61.17 ± 10.25	61.94 ± 7.82	0.819	57.25 ± 6.09	63.29 ± 9.13	0.097
Gender						
Female	7 (58.33%)	6 (35.29%)	0.274	6 (75.00%)	7 (33.33%)	0.092
Male	5(41.67%)	11 (64.71%)		2 (25.00%)	14 (66.67%)	
Initial BCVA (Letters)	37.42 ± 27.27	50.24 ± 31.89	0.269	18.63 ± 40.19	54.95 ± 18.24	0.002*
Initial IOP	14.67 ± 2.93	15.12 ± 3.33	0.709	14.13 ± 3.00	15.24 ± 3.19	0.402
Anti-VEGF injection times	9.00 ± 4.43	7.53 ± 4.32	0.379	9.88 ± 3.80	7.48 ± 4.45	0.189
Lens Status						
Phakic	9 (75.00%)	11 (64.71%)	0.694	7 (87.50%)	13 (61.90%)	
Pseudophakic	3 (25.00%)	6 (35.29%)		1 (12.50%)	8 (38.10%)	
* *p < 0.05*;						
BCVA: best-corrected visual acuity; CRT: central retina thickness; HbA1c: glycated hemoglobin; IOP: intraocular pressure;						
VEGF: vascular endothelial growth factor.						

Safety Outcomes

The mean final IOP (15.3 ± 3.2 mmHg) was not significantly higher than the baseline value (14.9 ± 3.1 mmHg, p = 0.5643), and not significantly higher than the IOP at one month after the last injection of ranibizumab (15.3 ± 3.3, p = 0.9985). The mean maximal IOP (the highest IOP recorded during follow-up) was 20.1 ± 4.7 mmHg, which was significantly higher than the baseline (14.9 ± 3.1 mmHg, p < 0.0001), but not significantly higher than the IOP at one month after the last ranibizumab injection (20.0 ± 4.5, mmHg, p = 0.8480). During the study, seven patients experienced IOP increases > 22 mmHg after DEX implant, but all these patients had IOP returned to ≤ 22 mmHg after being managed with topical IOP-lowering medications.

All patients tolerated the treatment well, and none experienced serious ocular (e.g., endophthalmitis, noninfectious endophthalmitis, vitreous hemorrhage, retinal tear, retinal detachment, or sustained IOP elevations) or systemic adverse events during the follow-up period.

Discussion

This retrospective case series, carried out in a tertiary medical center in central Taiwan, studied the therapeutic effects of DEX implant treatment on DME in eyes that had been unsuccessfully treated with intravitreal ranibizumab. In this study, DEX implants showed effectiveness for the treatment of DME. Patients were assessed at monthly intervals postoperatively, and anatomic improvements as gauged by CRT were sustained throughout the entire course of follow-up. Even though improvements in CRT did not correlate with significantly improved BCVA, neither did BCVA decrease over the course of treatment and follow-up. DEX implants were well-tolerated, with only a few cases of increased IOP that were manageable with antihypertensive eyedrops.

Currently, there is no optimal treatment regimen for DEX implant therapy for DME.[14] In the MEAD study, the protocol allows as-needed (*pro re nata*, PRN) retreatment with DEX implant with a frequency of no more than once every 6 months.[12] As the out-of-pocket expense for our patients was about 40,000 NTD (1,370 USD) for each DEX implant during the study, we treated most eyes with one dose of DEX implant, followed by PRN injections when macular edema reoccurred. During the mean follow-up of 7.4 ± 4.6 months, almost 80% of the patients received only one DEX implant, and only two eyes received three injections.

The various available treatments for DME include anti-VEGFs, laser, surgery, and corticosteroids, with each targeting different pathogenic mechanisms of the disease.[4] Our study suggests two main explanations for the observed benefit of DEX implant after unsuccessful ranibizumab treatment: the pharmacologic and pharmacokinetic properties of the DEX implant and the possible tachyphylaxis or tolerance to ranibizumab. First, inflammation plays a prominent role in the pathogenesis of DME. Many features of inflammation, such as the leukocyte recruitment and adhesion to vascular endothelium (leukostasis), increased blood flow and vascular permeability, tissue (macular) edema, neovascularization, and upregulation of inflammatory mediators, have been described in both human and animal models of diabetic retinopathy.[13–18] Intravitreally administered corticosteroids act to ameliorate DME in multiple ways. As established anti-inflammatory agents, they reduce the production of pro-inflammatory factors, limit vascular permeability, and inhibit the expression of VEGFs.[19] The DEX implant, a sustained-release drug delivery system for the potent corticosteroid dexamethasone, was developed to reduce the need for frequent intraocular injections due to the short half-life of intravitreally injected dexamethasone (< 4 hours).[20] The implant releases DEX into the vitreous for up to 6 months.[21] In a previous study, Lazic *et al.* demonstrated the therapeutic efficacy of DEX implant for DME resistant to the anti-VEGF bevacizumab.[22] The use of bevacizumab for DME is off-label, and therefore we examined patients who were initially treated with ranibizumab, which is FDA-approved for DME. Second, the patients' tachyphylaxis/tolerance to the previously administered ranibizumab might be another possible mechanism for the observed therapeutic effect after switching to intravitreal DEX implant. Even though there is a difference between tachyphylaxis and tolerance, both terms have long been presented as phenomena of reduced drug efficacy and are used synonymously in the literature.[23] Tachyphylaxis/tolerance in chronic treatment with bevacizumab and ranibizumab was first described in 2007 for age-related macular degeneration.[24,25] Tachyphylaxis/tolerance to ranibizumab might be a result of the neutralization of ranibizumab by the formation of circulating antibodies, the desensitization of the target tissue to the drug, or the reactivation of DME driven by another pathway.[26,27] These effects might be circumvented with the use of pharmaceuticals aiming at other DME-associated pathways.

In our study, DEX implant treatment showed a generally favorable safety profile. Historically, adverse events that are most commonly associated with corticosteroid therapy include cataracts and steroid-induced glaucoma. Although our study found DEX implants did not seem to have caused cataract in any of the patients, the mean follow-up period was ~ 7 months, which may not be sufficient for the development of cataracts. Some patients in this study experienced transient increase in IOP that were successfully managed with topical medication. There was no case of serious ocular or systemic adverse events such as endophthalmitis, noninfectious endophthalmitis, vitreous hemorrhage, retinal tear, retinal detachment, or sustained IOP elevations.

In this study, we found three clinical factors correlated with the treatment responses. Our results suggested that patients with lower baseline HbA1c had better anatomic improvement after treatment. The importance of glycemic control in the

management of diabetic retinopathy was emphasized by previous studies.[28, 29] The other two baseline predictive factors were thicker CRT and worse BCVA. Both factors correlated with better responses to DEX treatment in their respective aspects. Campos *et al.* also found that lower baseline BCVA predicted a higher visual acuity gain.[30] It may be suggestive of a 'ceiling effect' and can't be ruled out completely in this prediction model; that is, smaller improvements are required to achieve good vision in patients with better starting vision, while those with lower BCVA at baseline have greater capacity to achieved better vision outcome. Another limit of visual acuity improvement was the uncertant optimal timing for DEX switching in patients with DME non-responder to intravitreal ranibizumab. If we could know the patient with DME who is more appropriate receiving DEX implant, and perform early switch to DEX implant, that may improve their visual acuity outcome more.Limitations of this study include the small sample size and short-term follow-up, the uncontrolled retrospective design of the study, the nonstandard treatment protocols, and a lack of consistent performance of fluorescein angiography prior to switching to DEX implant treatment. Nevertheless, this study showed that intravitreal DEX implant treatment was effective immediately after switch and safe in cases of refractory DME resistant to ranibizumab. Switching to DEX implant can be considered in eyes with DME that do not respond to anti-VEGF treatments. Furthermore, higher baseline CRT and worse BCVA were found to be the predictive factors for better therapeutic responses. However, further studies are necessary to determine the optimal timing for DEX switching in patients with DME non-responder to intravitreal ranibizumab and to shed light on the long-term outcomes of this treatment modality.

Conclusion

This study demonstrated the feasibility of switching to intravitreal DEX implant in cases of DME that are non-responder to intravitreal ranibizumab treatment. In patients with refractory DME after ranibizumab, conversion to DEX implant treatment resulted in a significant improvement in CRT but not in BCVA. Nevertheless, higher baseline CRT and worse BCVA can predict better therapeutic responses.

Abbreviations

DEX: dexamethasone, DME: diabetic macular edema, BCVA: best-corrected visual acuity, CRT: central retinal thickness, IOP: intraocular pressure, VEGF: vascular endothelial growth factor, BRB: blood-retinal barrier, FDA: Food and Drug Administration, HbA1c: glycated hemoglobin, ETDRS: Early Treatment Diabetic Retinopathy Study, GLMM: generalized linear mixed model.

Declarations

Ethics approval and consent to participate.

This study was approved by the Institutional Review Board of China Medical University Hospital, Taiwan. The need for approval was waived due to deidentification.

Consent for publication

Written informed consent for publication of his clinical details and clinical images was obtained from the patient.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Hsia NY, Lin CJ, Chen HS, Chang CH, Lai CT, Lin JM, Chen WL, Tien PT, Tsai YY were responsible for substantial contributions to the conception or design of the work, and acquisition of data. Lin CJ, Chen HS, Chang CH were responsible for interpretation of results. Hsia NY, Lin CJ, Bair H participated in the design and was a major contributor in writing the manuscript. Hsia NY, Lin CJ, Bair H, Chen WL, Wu WC were responsible for final approval of the version to be published. All authors reviewed and approved the final manuscript.

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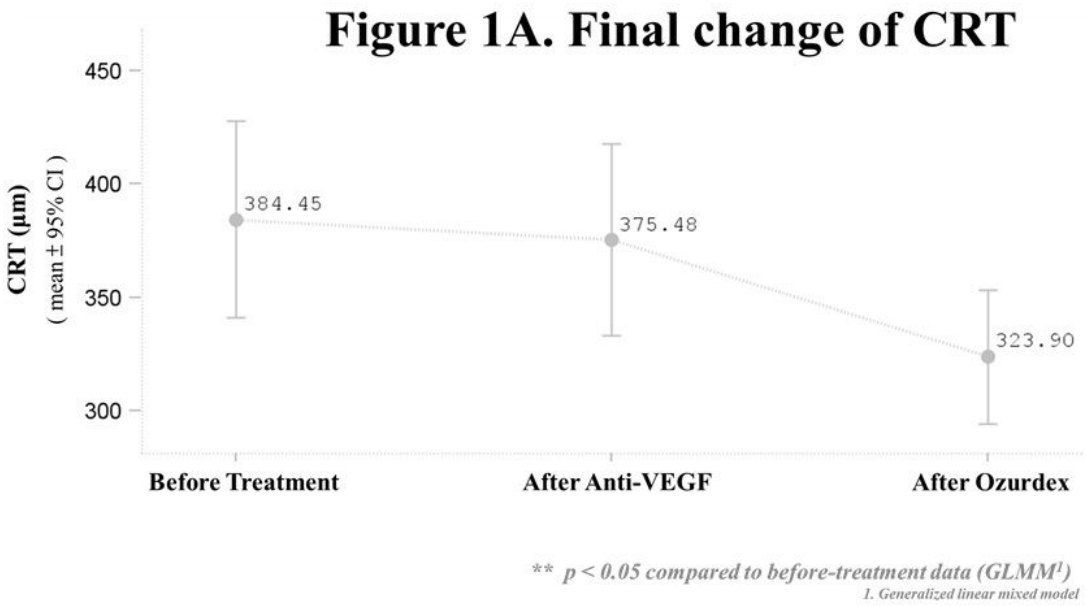
Figures



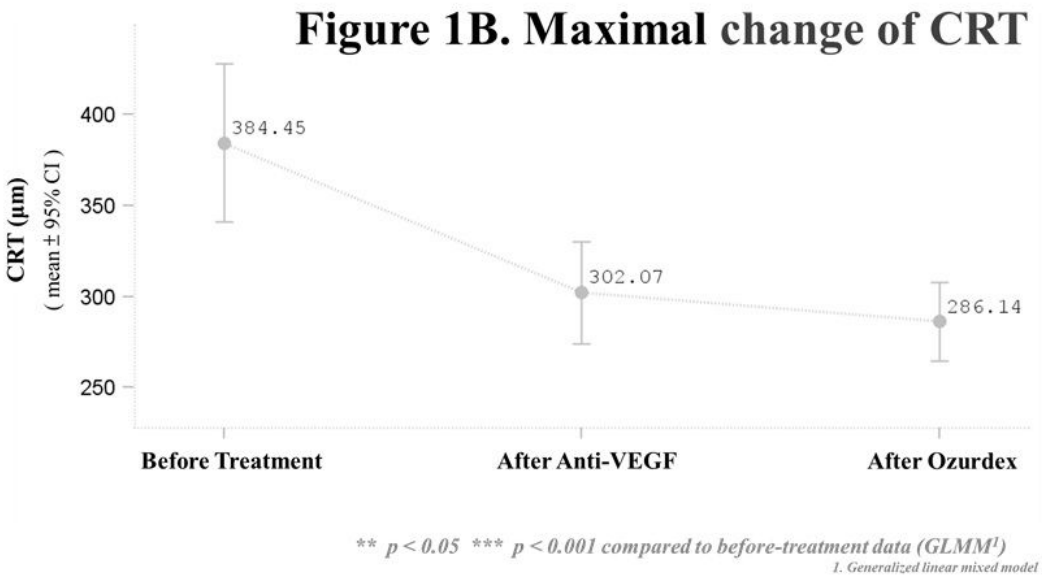
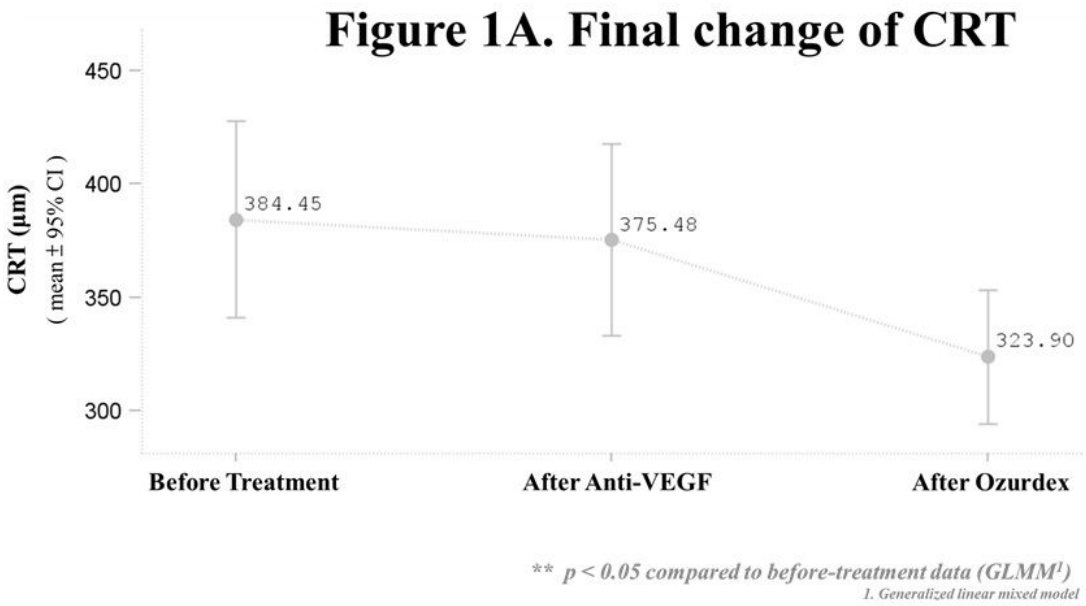
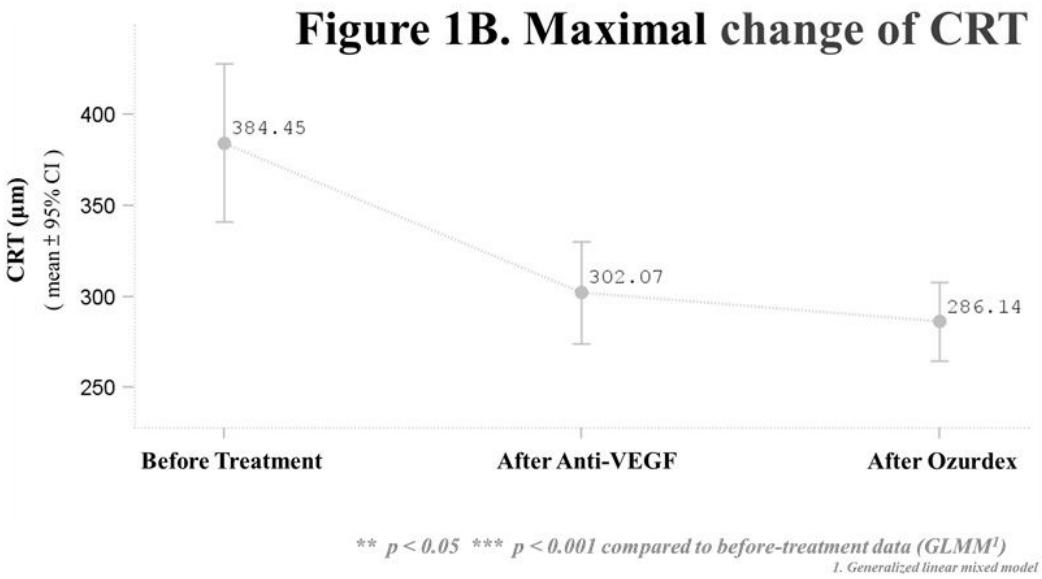


Figure 1

A. Mean baseline and final CRT after the respective treatments. The mean final CRT after DEX implant treatment was significantly lower than the CRT ($p = 0.0249$) at baseline and one month after the last ranibizumab injection ($p = 0.0265$). B. Mean best CRT (the lowest CRT value recorded during follow-up) at baseline and after the respective treatments. The mean best CRT after DEX implant treatment was significantly lower than the CRT ($p < 0.0001$) before treatment.





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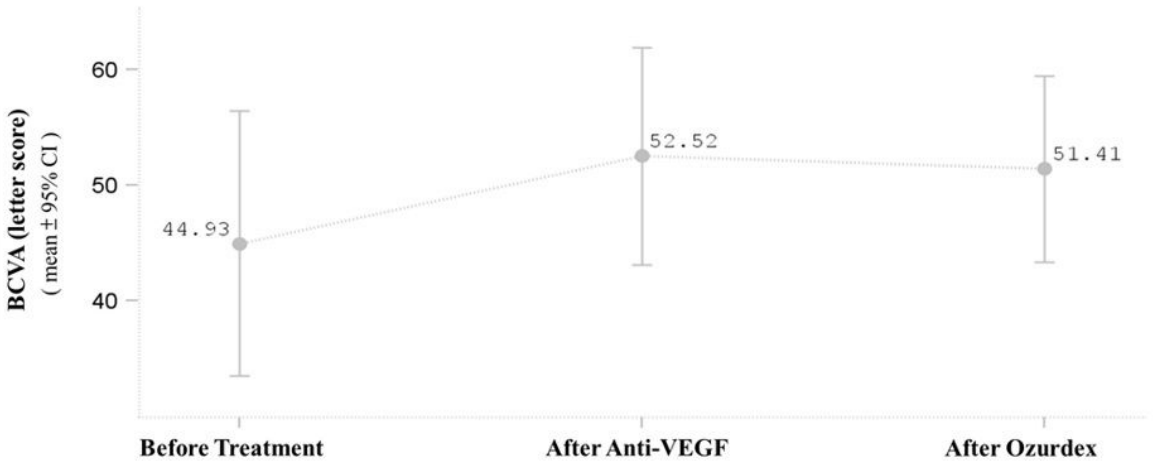


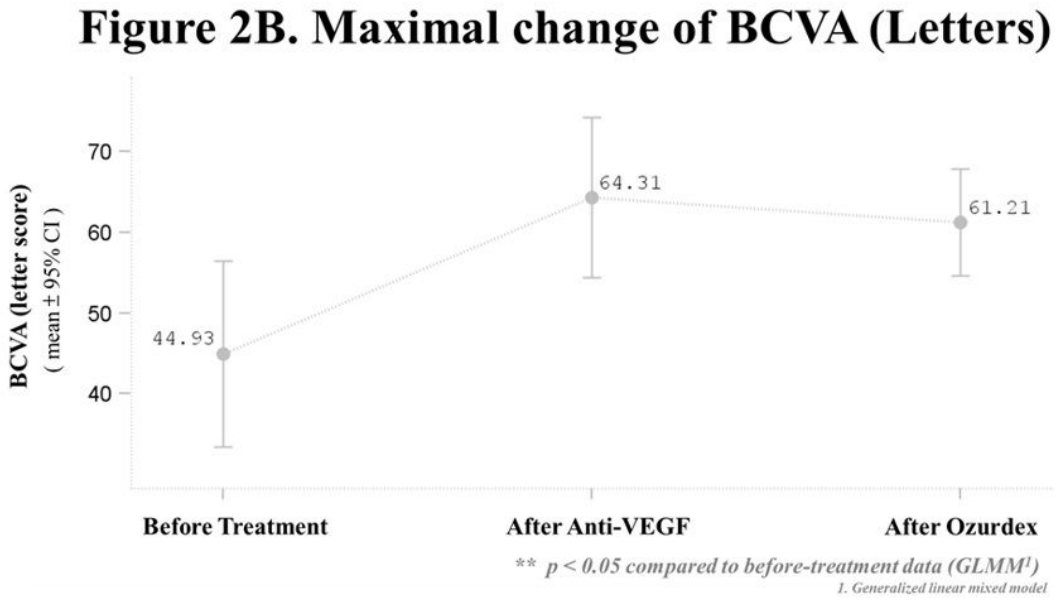
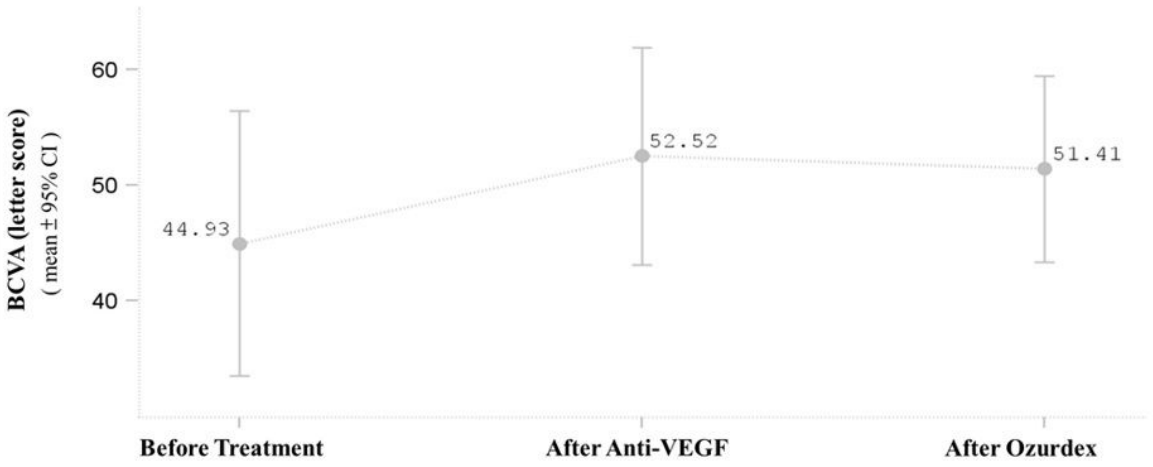
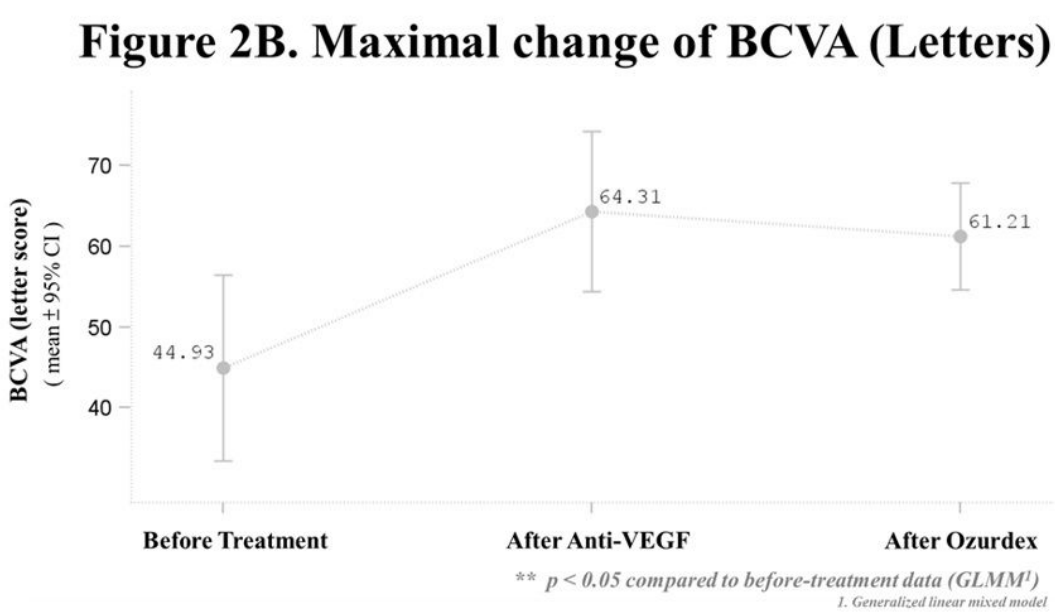


Figure 2

A. Mean BCVA at baseline and after the respective treatments. There was no significant improvement in BCVA one month after the last ranibizumab and after DEX implant treatment. B. Mean maximal BCVA (the highest letter score recorded during follow-up) at baseline and after respective treatments. The mean maximal BCVA after DEX implant treatment was significantly higher than baseline BCVA (p = 0.0022).





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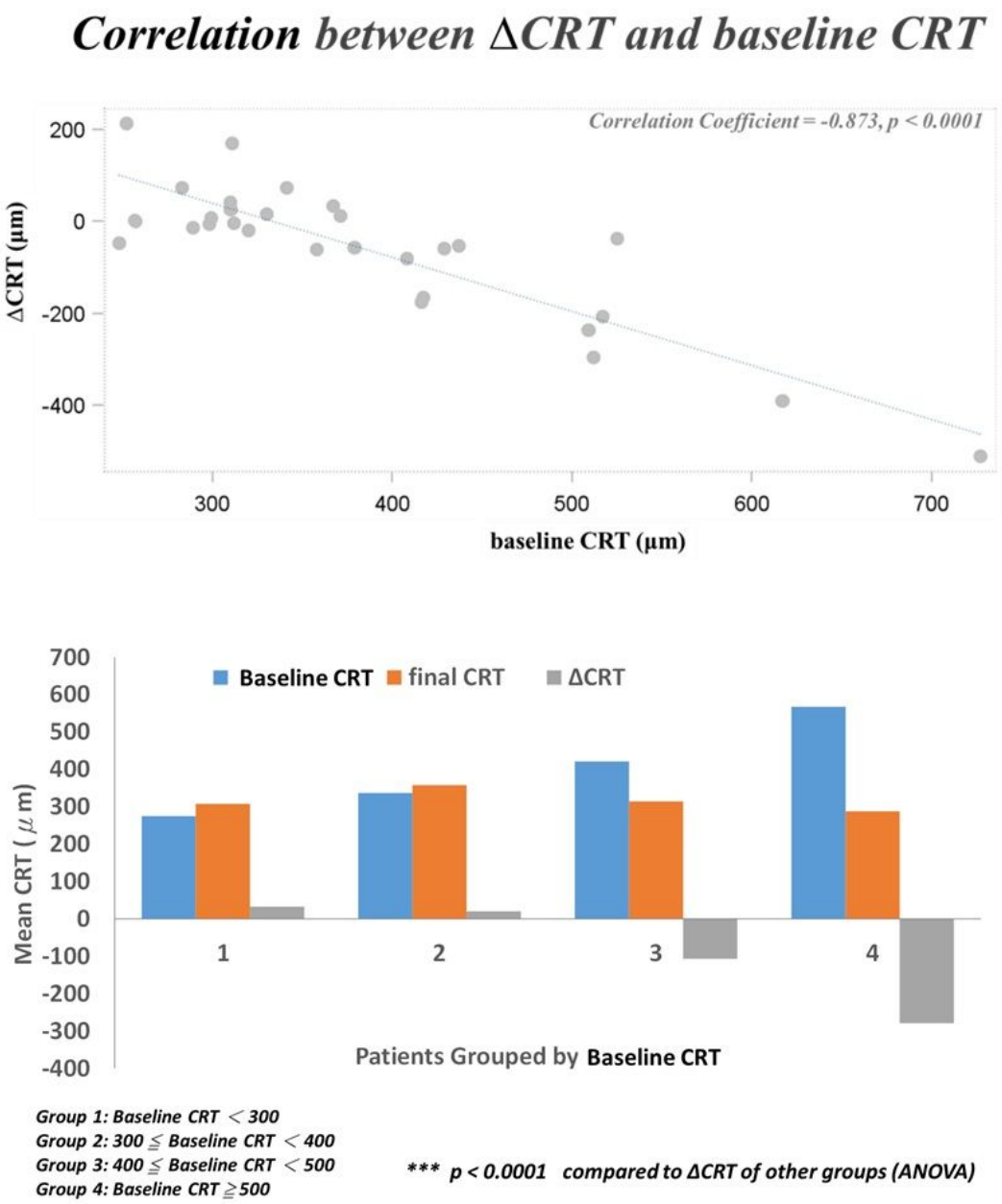
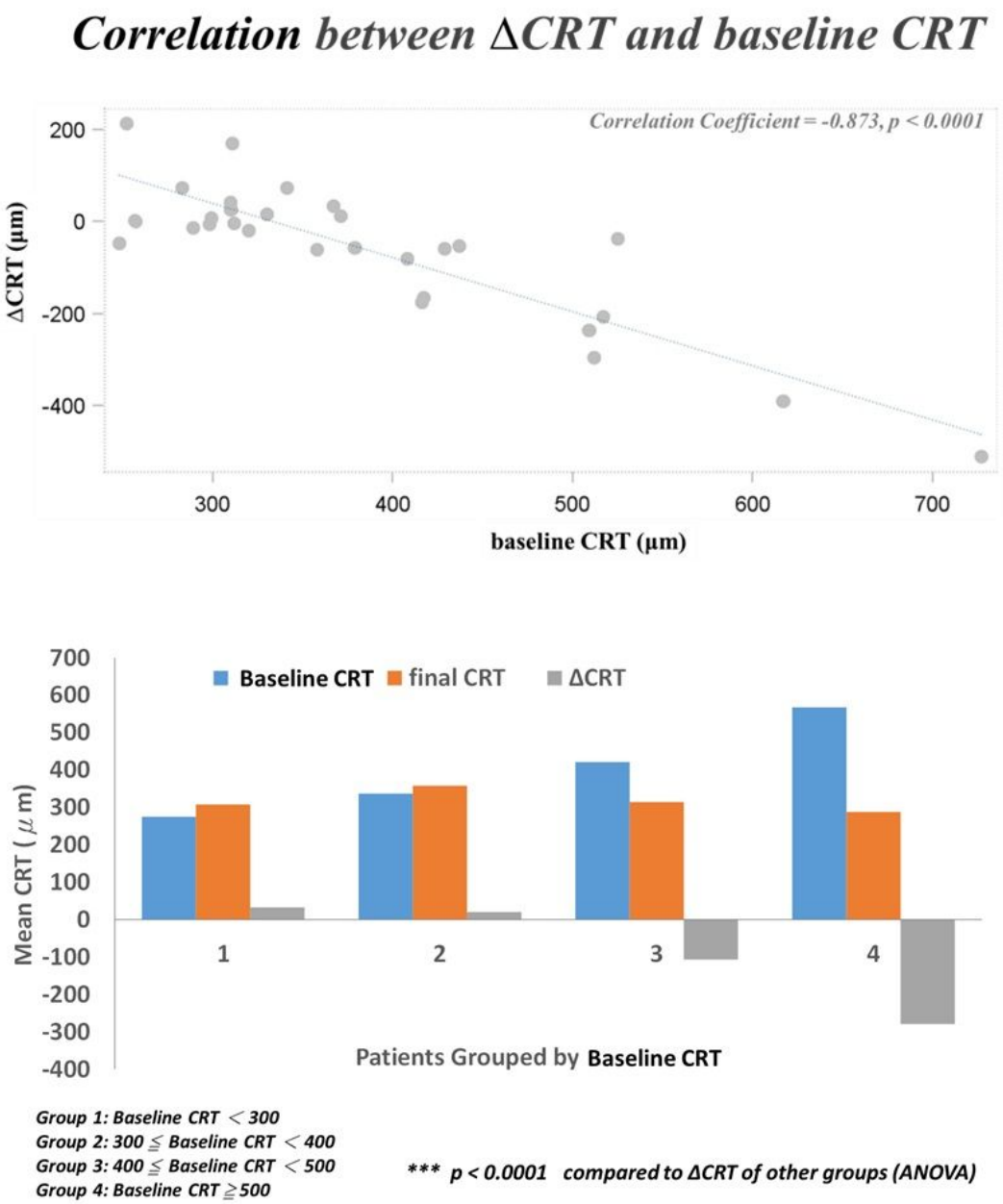


Figure 3

Correlation between changes in CRT and baseline CRT.



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Correlation between changes in CRT and baseline CRT.

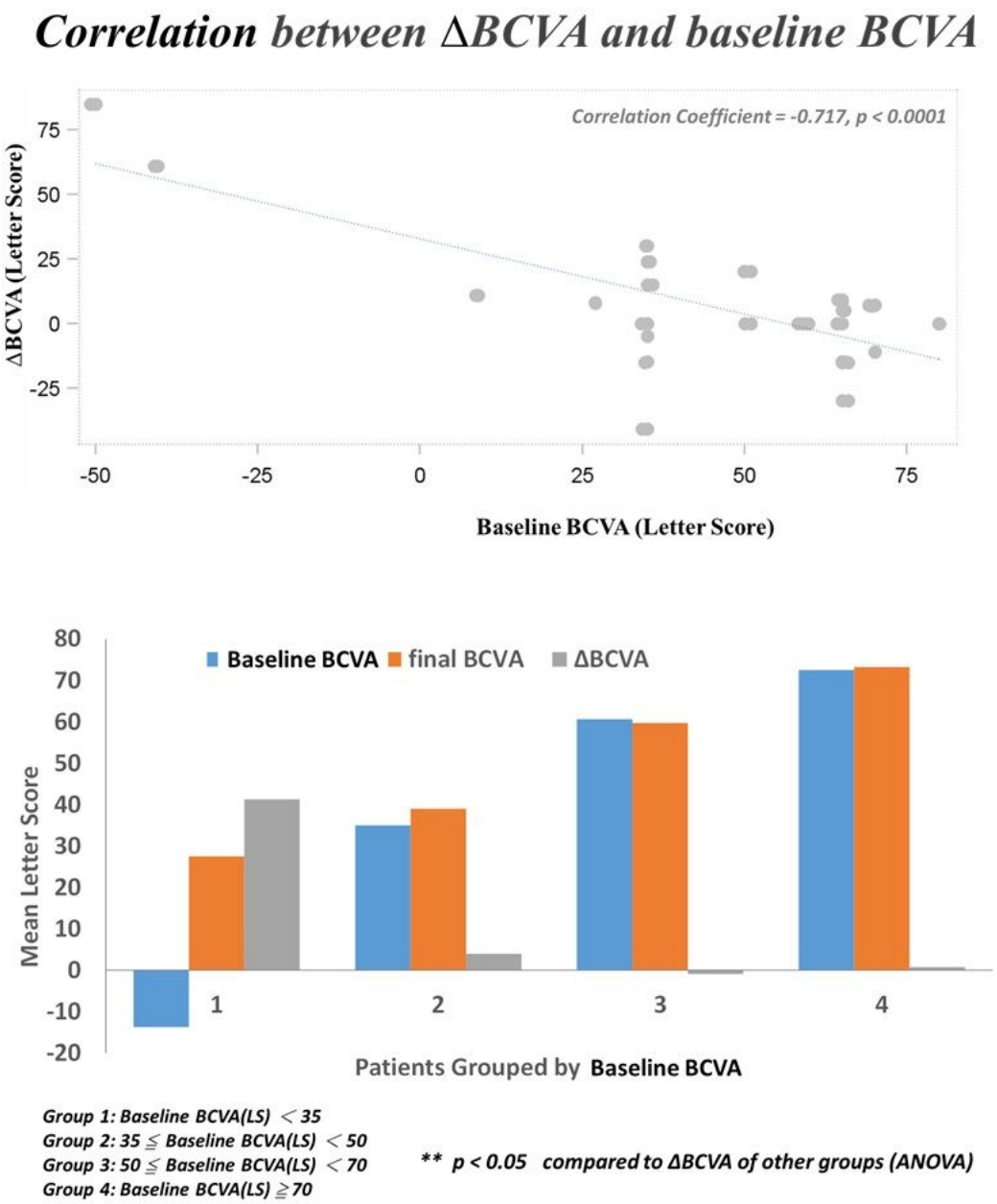

Figure 4

Correlation between changes in BCVA and baseline BCVA.

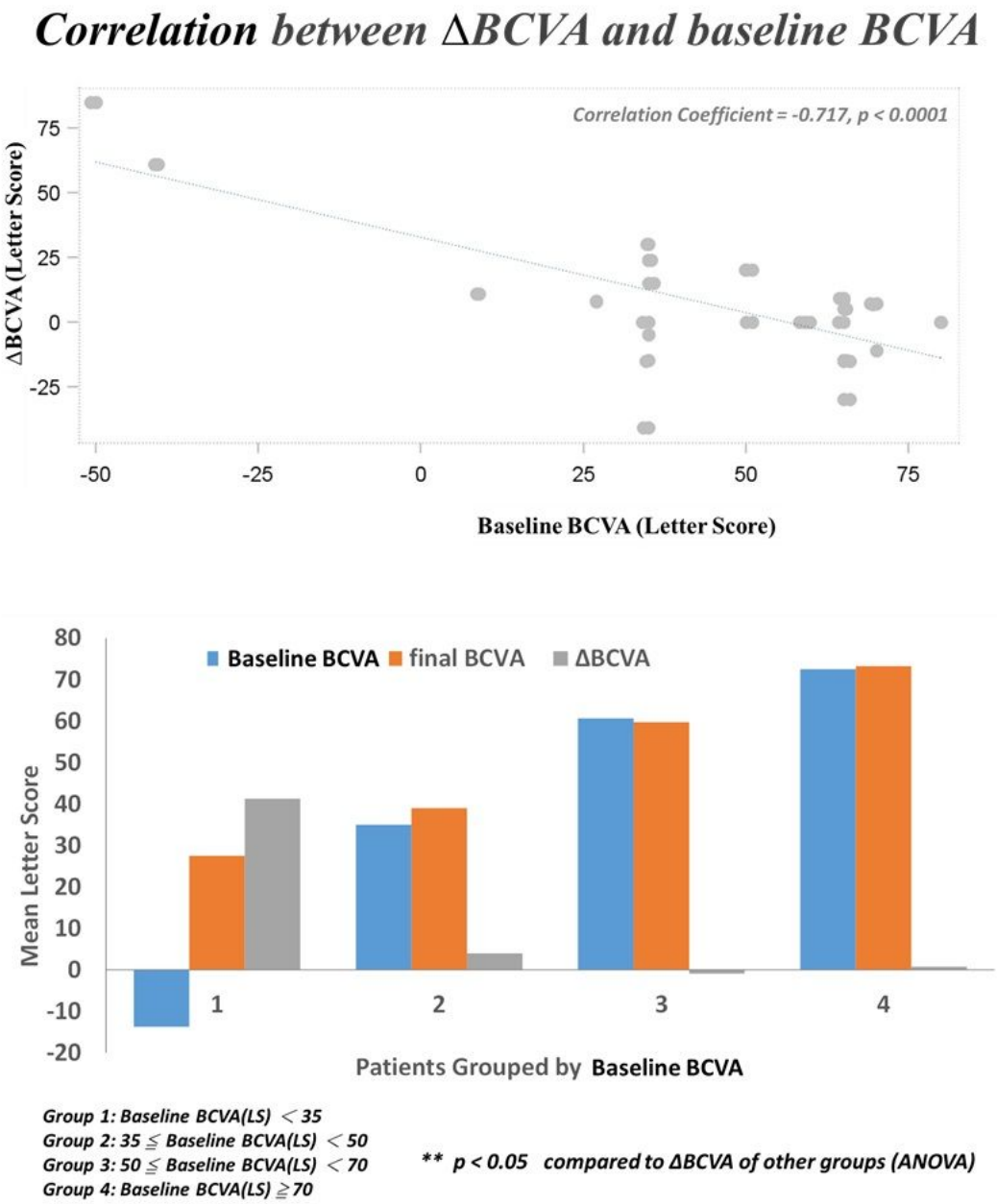

Figure 4

Correlation between changes in BCVA and baseline BCVA.