Correlation of retinal layer changes with vision gain in diabetic macular edema during conbercept treatment

CURRENT STATUS: ACCEPTED

BMC Ophthalmology • BMC Series

Yupeng Xu
Shanghai Jiao Tong University

Yuan Qu
Shanghai Jiao Tong University

Yan Suo
Shanghai Jiao Tong University

Jian Gao
Anhui Medical University

Xia Chen • tracy_chen1990@hotmail.com
Shanghai Jiao Tong University

Corresponding Author
ORCID: 0000-0002-1077-3133

Kun Liu
Shanghai Jiao Tong University

Xun Xu
Shanghai Jiao Tong University

DOI:
10.21203/rs.2.343/v1

SUBJECT AREAS
Internal Medicine Specialties

KEYWORDS
Diabetic macular edema, retinal layer thickness, layer segmentation, anti-VEGF, Conbercept
Abstract

**Backgrounds:** To assess the changes in individual retinal layer thickness and visual function associated with gains in visual acuity after an intravitreal conbercept injection in the diabetic macular edema (DME) on spectral domain optical coherence tomography (SD-OCT) and microperimetry during 1-year follow-up.

**Methods:** Retrospective observational study. Twenty patients with clinically significant DME in the study eye were imaged by SD-OCT every three months and MP1 microperimeter in the third month while receiving anti-vascular endothelial growth factor (VEGF) (conbercept) treatment. In each patient, seven retinal layers were segmented in 98 scans covering a 6mm×6mm area of the macula at baseline and during 1 year of treatment. An automatic, full-threshold microperimetry of the central field (10°×10°, 40 stimulated points) with the MP1 microperimeter. Thickness and microperimetry changes were quantitatively measured and evaluated for their correlation with increases in visual acuity.

**Results:** Although thicknesses of the inner nuclear layer (INL) and the outer nuclear layer (ONL) were reduced the most after treatment (p< 0.05), decreases of the ganglion cell layer (GCL) (r = 0.591, p= 0.006) and inner plexiform layer (IPL) (r= 0.663, p= 0.001) in central subfield area was associated with best-corrected visual acuity (BCVA) gain, and had the best estimation of BCVA gain (adjust R2=0.544). Mean macular sensitivity in the central subfield was also well correlated with BCVA gain (r=0.531, p=0.016).

**Conclusions:** Whereas the largest decrease of layer thickness occurred in the INL and ONL, the decreases in GCL and IPL were more associated with gains in vision and improved microperimetry. The decrease of the GCL and IPL might suggest that neural recovery occurred after the resolution of edema during conbercept treatment.

**Keywords:** Diabetic macular edema, retinal layer thickness, layer segmentation, anti-
VEGF, Conbercept.

Background

Diabetic retinopathy (DR) is one of the leading causes of vision loss among working-aged adults globally(1). Of the estimated 382 million people with diabetes mellitus worldwide (2), approximately 35% have signs of DR; of these, a further one third of DR cases are vision-threatening DR, most of which are diabetic macular edema (DME)(3). Prolonged hyperglycemia in DME patients causes hypoxia and inflammation, resulting in an upregulation of growth factors and cytokines, e.g. vascular endothelial growth factor (VEGF) (4) which is essential for causing vascular leakage and acts as a proinflammatory cytokine in the pathogenesis of DME(2); thus, the intravitreal anti-VEGF injection is now a standard treatment for DME(5).

The evaluation of retinal microstructures by spectral domain optical coherence tomography (SD-OCT) allows quantitative analysis of DME(6). Total retinal thickness has often been used to monitor treatment effectiveness of anti-VEGF therapy for DME (7, 8). Changes in the individual retinal layer might serve as a biomarker for response to treatment (9). A recent study compared the changes in layer thickness of DME patient after 1-year of intravitreal ranibizumab or triamcinolone and found that the decrease in retinal nerve fiber layer (RNFL) may have a possible impact on best-corrected visual acuity (BCVA) gain(10).

Conbercept (KH902; Chengdu Kanghong Biotech Co., Ltd., Sichuan, China) is a recombinant fusion protein that was designed as a receptor decoy and has high affinity for all VEGF isoforms and placental growth factor (PIGF)(11); it is widely used in anti-VEGF therapy in China(12, 13). To the best of our knowledge, no study has examined the effect of conbercept on individual layer changes in DME treatment.

Also, limited previous studies exam the function of retinal ganglion cells with combination
to the BCVA changes and layer thickness changes. As signs of neurodegeneration are also prevalent in patients with diabetes, the impact of intravitreal medication on functional changes in macular needs to be investigated in detail. Microperimetry was widely used in the previous studies to exam the function of retinal ganglial cell (RGC) in macular and thus could be used as a biomarker of RGC function(14, 15).

This study aimed to measure the thickness from all retinal layers during 1-year follow-up to find correlations between visual acuity recovery and retinal layer thickness changes purely from the treatment effect. Microperimetry examination was also performed to further exam the function of RGC changes with BCVA gain. Our study might provide a new view on what might happen after 1-year treatment of anti-VEGF therapy with conbercept.

Methods

Study Design

This study is a retrospective single-center observational study. This study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Shanghai General Hospital (No. 2016KY003). Data were obtained from the database of ophthalmology in Shanghai General Hospital. Written informed consent was obtained from all subjects.

Participants

Patients with untreated clinically significant DME in the study eye without previous anti-VEGF drug or steroid treatment and without clinically significant macular edema in fellow eye were included in the study. A central subfield thickness of 320 μm for males and 305 μm for females was followed for clinically significant macular edema (for Heidelberg device)(16). Intravitreal conbercept (0.5 mg/0.05 mL) injections were performed by one retinal specialist. Patients were followed-up for 12 months between August 2010 and December 2013. All patients received three injections in the first three months, and then a
pro re nata (PRN) strategy was then followed. Each patient underwent a thorough ophthalmic examination, including BCVA, slit lamp observation, and SD-OCT measurements, before the first injection and at each follow-up visit. The exclusion criteria were the following: (1) any non-diabetes-related macular edema; (2) any ophthalmological or neurological disease that could affect or could have affected the visual acuity (uncontrolled glaucoma, uveitis, retinal macular traction or macular epiretinal membrane); and (3) an eye with a history that could potentially affect the retinal layer thickness, e.g., vitrectomy, laser photocoagulation and cataract extraction.

The BCVA was tested at baseline and monthly thereafter using Early Treatment Diabetic Retinopathy Study (ETDRS) charts at 4 meters. The serum glycated hemoglobin level was assessed at baseline.

**Optical Coherence Tomography**

A 5.4×5.4-mm area of the macular region centered on the fovea was examined by the Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany) with display mode; volume scans of 97 sections were centered on the fovea, and 5 B-scan images at each section were averaged. For standardization, all examinations were performed by one well-trained technician who was masked to the identity of the subjects and was not involved in the data analysis. A build-in automatic recognition system enabled scanning of precisely the same location during the follow-up examinations.

To identify eyes/patients with increased thickness in the central subfield, the protocol proposed by DRCR.net was followed. Foveal thickness was manually segmented by one retinal specialist (Y.S.) using the SD-OCT software (Spectralis version 6.3.2.0, Heidelberg Engineering, Heidelberg, Germany). All scans of a particular eye were graded consistently by the same reader to counteract a potential annotation bias. The whole retina was divided into three circles as follows: central subfield (diameter of 1 1000μm) and inner
(diameter of 3000μm) and outer (diameter of 6000μm) rings. The inner and outer rings were divided into the superior, inferior, nasal and temporal regions, and the average retinal thickness in these total 9 regions was measured automatically. The Heidelberg Software recognizes retinal tissue interfaces and, using these landmarks, allows the software to handle the following retinal layers: retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), and the photoreceptor-retinal pigment epithelium complex (PR). All layers were first segmented using the built-in automated software, and manual correction of artifacts was then performed to obtain precise results.

*Microperimetry Examination*

Microperimetry was performed on all subjects using the MP1 Microperimeter. (version 1.7.0., Nidek Technologies, Gamagori, Japan) in the first visit and the 3-month follow-up after injection. To avoid bias resulting from instrument variability, all examinations were calibrated accurately by the same experienced technician. The following parameters were used: a fixation target consisting of a red ring 2° in diameter; white, monochromatic background at 4asb, stimulus size Goldman III with 200ms projection time; Stimulus light attenuation was set at 10dB, with a threshold 4-2-1 strategy (14, 15).

A macular 10° program is applied, in which 40 stimuli was used: the central 2° area (diameter of 600μm) covered with 8 stimuli; superior, inferior, nasal and temporal areas were each targeted with 4 stimuli (totally 32 stimuli) located 6° (diameter of 1800μm) and 10° (diameter of 3000μm) from the center of the fovea. Mean sensitivity were calculated in central area (diameter=1000μm) and the four quadrants in the inner ring (diameter=3000μm).

*Statistical Analyses*

All statistical analyses were performed using SPSS version 18.0 for Windows software
(SPSS, Chicago, IL, USA). All continuous results are expressed as the mean ± standard
deviation. The changes of retina thickness at baseline and after one year follow-up on
each region of each layer were compared by paired t-test. Correlations between the OCT
parameters changes and injection times were evaluated using Spearman correlation
coefficients because the injection times were not normally distributed while all the other
parameters were evaluated using Pearson correlation coefficients. We consider $r>0.5$ as
well positively correlated and $r= 0.3$ to 0.5 as moderate positively correlated. Univariate
linear regression and stepwise backward multivariate linear regression analyses were
performed to evaluate the contribution of each characteristic to BCVA gain at month 12
compared to baseline, and $p< 0.05$ was considered significant.

Results

Demographic and clinical characteristics

Twenty patients with DME, including 10 men and 10 women, were evaluated. The baseline
characteristic was revealed in Table 1. The mean age of patients with DME was $60.55±$
8.65 years old. The serum glycated hemoglobin level was $7.13± 0.99\%$. Intraocular
pressure was $15.79± 2.95\text{mmHg}$. Seven patients had hypertension. All patients were
treated with conbercept monotherapy. The mean baseline visual acuity (EDTRS) of the
treated eye was $57.50± 12.50$ letters and increased by an average of $8.65$ letters to
$66.15± 14.47$ letters at month 12 ($p< 0.001$). The average total retina thickness of the
whole EDTRS grid decreased from $387.47± 88.08 \mu$m at baseline to $347.44± 60.78\mu$m at
month 12 ($p= 0.003$). The mean macular sensitivity increased from $8.17± 3.66\text{db}$ to $9.50±$
4.18db after three months ($p= 0.008$). On average, patients received 6.60 intravitreal
injections of conbercept during the one-year treatment.

Changes in different layers’ thicknesses in one year of conbercept treatment

The center total retina thickness decreased from $482.05± 156.98 \mu$m at baseline to $336±$
92.84 μm at month 12 by an average of 146.05 μm (p= 0.002). The thickness changed more significantly within the inner ring than in the outer ring of the EDTRS grid (p< 0.05). The average thickness of inner ring decrease by an average of 75.20μm and outer ring decreased by an average of 33.58μm.

The treatment effect of conbercept is reflected in decrease in thickness in each individual retinal layer in one year of treatment. The average thickness of all layers became significantly thinner (p< 0.05). In the central subfield area, all the layer thicknesses were decreased while the INL, OPL and ONL layers had significant changes. Furthermore, when analyzing inner and outer ring, we found the inner superior section had the most significant changes in the most layers (Figure 1). The layer thickness changes of the other regions are illustrated in Figure S1&S2.

Correlation of individual layer changes with BCVA gain in different regions

The correlations of individual layer changes and other potentially important explanatory variables with BCVA gains were explored (Table 2). Decrease in GCL, IPL and RNFL thickness in central subfield corrected well with BCVA gain. (r= 0.591, 0.663 and 0.558, respectively). Besides, nasal part of IPL thickness both in inner ring and outer ring correlated well with BCVA gain (r=0.552 and 0.678), while other layers did not show good correlation with BCVA gain in nasal part.

A multivariate analysis was further conducted for these subsets of data. In the univariate analysis, the decreases in some individual retinal layers’ thickness were associated with larger BCVA gains. These findings were confirmed in the multiple linear regression (Table 3). In our cases, the best multivariate linear mode for predicting the BCVA gain included the thickness decreases of the IPL and GCL in the central subfield. The coefficient of determination R² for this model was 0.544, outperforming all the other models. In this model, decrease in GCL and IPL were important factors that associated with final BCVA
Correlation of microperimetry changes with BCVA gain in different regions

To further analyze the possible reason of this phenomenon, microperimetry analysis were performed after injection. The mean baseline visual acuity (EDTRS) of the treated eye increased by an average of 9.35 letters to 66.85± 10.17 letters at month 3(p< 0.001). Baseline mean macular sensitivity in different regions were 4.60±2.95db (central subfield), together with 8.59±3.92 db(superior), 8.79±4.54 db (inferior), 9.80±4.92 db (nasal) and 9.09±4.19 db (temporal) in inner ring. Only increase of mean sensitivity in central subfield corrected well with BCVA gain (r= 0.531, p=0.016) (Table 4).

Discussion

Intravitreal conbercept has been shown to be effective in the treatment of proliferative diabetic retinopathy and age-related macular degeneration, resulting in reduced central retinal thickness and improved BCVA in the treated eyes(12, 17). The anti-VEGF drug conbercept was found to suppress the high glucose-induced migration and sprouting of human retinal endothelial cells by blocking VEGF and PIGF, thereby restoring capillary integrity (18). Reduced vascular leakage results in the resolution of retinal fluid. Decreased retinal layer thickness would be the obvious consequence and is indeed observed in most layers and associated with improved visual acuity. We found that the decreases in GCL and IPL were the best correlated with BCVA gain, although the retinal thickness decreased the most in the INL and ONL layers, where cystoid space and swelling are mainly located (19). explained by the neural recovery in the GCL and IPL layers. The RGC recovery was further proved in the Microperimetry results as the mean sensitivity gain in central subfield was correlated with BCVA gain after anti-VEGF injection.

Visual acuity gain was best correlated with the decreases in the GCL and IPL layer thickness. In our retrospective study, the changes in individual layer thickness from fellow
eye were measured to compare the damage from the same level of hyperglycemia to the study eye, in which the center subfield and inner ring did not have significant changes (Figure S3). Although GCL degeneration in diabetic patients has been previously described as an early-onset issue accompanying hyperglycemia (20) and microvascular abnormalities (21), our findings suggested that the effectiveness of conbercept in reducing edema which suggests possible intraretinal fluid accumulation (22). Conbercept might provide benefit on neural recovery in the GCL and IPL layers by improving the metabolic supply with the resolution of subretinal fluid.

Interestingly, our study showed that the layer thickness of ONL, INL and OPL had significant changes during one year while these layers did not significant associate with the final BCVA gain. This might be explained as follows: in the early stages of DME development, a thickness increase occurs predominantly in the INL, probably due to colocalization of the deep retinal vascular net and the extracellular accumulation of fluid due to alterations of the blood-retinal barrier in these retinal capillaries (22). The development of clinical macular edema in diabetes might be associated with structural damage of the remaining retinal layers, which allows an increased accumulation of fluid in the retinal layers located in ONL (23). We suggested that there might be more primary nuclear damage in the baseline of our study. Nuclear cells that have already gone into apoptosis will not recuperate through resolution of subretinal fluid. Our hypothesis was further proved in the model used to predict final vision, where the decreases in the INL and ONL layers had negative correlations with final vision.

A ceiling effect was also found in the baseline BCVA, which contributes negatively in the model predicting visual acuity gain. This finding indicates that eyes starting with good visual acuity gain fewer letters because there is less room for improvement (24). A similar finding was also reported in other studies, where patients with better visual acuity at
baseline gained fewer letters than patients with low visual acuity at baseline (25).

There are some limitations in the present study. First, the retrospective nature and relatively small sample size might have hindered the potential associations. Furthermore, the automated segmentation of retina layers in pathologic conditions is not reliable and is prone to artifacts (26). The analysis algorithms are manufacturer-specific, and differences exist between devices (27). Manual correction is necessary to add a subjective component to the quantification. Better segmentation software will be needed for a large population study.

Conclusions

To our knowledge, this is the first study to segment seven individual layers in the center retina during conbercept therapy, measuring treatment response both in BCVA and microperimetry respects. Edema reduction of GCL and IPL layer after conbercept therapy had the strongest correlation with recovery in visual acuity and sensitivity. Segmentation of ganglion cell layer and inner plexiform layer seemed to be of greater clinical importance for monitoring treatment response of conbercept therapy in DME patients than other layers.

Abbreviations

**DME**: Diabetic macular edema

**SD-OCT**: Spectral domain optical coherence tomography

**VEGF**: Vascular endothelial growth factor **INL**: Inner nuclear layer

**ONL**: Outer nuclear layer **GCL**: Ganglion cell layer **IPL**: Inner plexiform layer

**BCVA**: Best-corrected visual acuity **DR**: Diabetic retinopathy

**RNFL**: Retinal nerve fiber layer **PIGF**: Placental growth factor

**RGC**: Retinal ganglial cell **PRN**: pro re nata
ETDRS: Early Treatment Diabetic Retinopathy Study ONL: outer nuclear layer

PR: photoreceptor-retinal pigment epithelium complex

Declarations

Ethics approval and consent to participate
This study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Shanghai General Hospital (No. 2016KY003). Written informed consent was obtained from all subjects.

Consent for publication
Not applicable in this study.

Availability of data and material
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

Funding
This study was supported by National Natural Science Foundation (Grant No.: 81470638) and Project of National Key Research Program on Precision Medicine (Grant No.: 2016YFC0904800). They supported in the data collection, interpretation and writing the manuscript.

Authors' contributions
KL and XX designed this study and performed the intravitreal injections. JG and YS collected and analyzed the data and generated the figures. YX and YQ involved with the manuscript development and proofreading. XC reviewed and revised the manuscript. YX and XC approved the final version of the manuscript. All authors read and approved the final manuscript.
Acknowledgements

Not applicable in this study.

References

1. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet. 2010;376(9735):124-36.
2. Das A, McGuire PG, Rangasamy S. Diabetic Macular Edema: Pathophysiology and Novel Therapeutic Targets. Ophthalmology. 2015;122(7):1375-94.
3. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes care. 2012;35(3):556-64.
4. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005;54(6):1615-25.
5. Jampol LM, Bressler NM, Glassman AR. Revolution to a new standard treatment of diabetic macular edema. Jama. 2014;311(22):2269-70.
6. Browning DJ, Glassman AR, Aiello LP, Bressler NM, Bressler SB, Danis RP, et al. Optical coherence tomography measurements and analysis methods in optical coherence tomography studies of diabetic macular edema. Ophthalmology. 2008;115(8):1366-71, 71 e1.
7. Schmidt-Erfurth U, Lang GE, Holz FG, Schlingemann RO, Lanzetta P, Massin P, et al. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study. Ophthalmology. 2014;121(5):1045-53.
8. Brown DM, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. Ophthalmology. 2013;120(10):2013-22.
9. Byeon SH, Chu YK, Hong YT, Kim M, Kang HM, Kwon OW. New insights into the
pathoanatomy of diabetic macular edema: angiographic patterns and optical coherence tomography. Retina (Philadelphia, Pa). 2012;32(6):1087-99.

10. Prager SG, Lammer J, Mitsch C, Hafner J, Pemp B, Scholda C, et al. Analysis of retinal layer thickness in diabetic macular oedema treated with ranibizumab or triamcinolone. Acta ophthalmologica. 2018;96(2):e195-e200.

11. Wang Q, Li T, Wu Z, Wu Q, Ke X, Luo D, et al. Novel VEGF decoy receptor fusion protein conbercept targeting multiple VEGF isoforms provide remarkable anti-angiogenesis effect in vivo. PloS one. 2013;8(8):e70544.

12. Li X, Xu G, Wang Y, Xu X, Liu X, Tang S, et al. Safety and efficacy of conbercept in neovascular age-related macular degeneration: results from a 12-month randomized phase 2 study: AURORA study. Ophthalmology. 2014;121(9):1740-7.

13. Zhang Z, Yang X, Jin H, Qu Y, Zhang Y, Liu K, et al. Changes in Retinal Nerve Fiber Layer Thickness after Multiple Injections of Novel VEGF Decoy Receptor Conbercept for Various Retinal Diseases. Scientific reports. 2016;6:38326.

14. Midena E, Vujosevic S, Cavarzeran F, Microperimetry Study G. Normal values for fundus perimetry with the microperimeter MP1. Ophthalmology. 2010;117(8):1571-6, e1.

15. Midena E, Vujosevic S, Convento E, Manfre A, Cavarzeran F, Pilotto E. Microperimetry and fundus autofluorescence in patients with early age-related macular degeneration. The British journal of ophthalmology. 2007;91(11):1499-503.

16. Chalam KV, Bressler SB, Edwards AR, Berger BB, Bressler NM, Glassman AR, et al. Retinal thickness in people with diabetes and minimal or no diabetic retinopathy: Heidelberg Spectralis optical coherence tomography. Investigative ophthalmology & visual science. 2012;53(13):8154-61.

17. Su L, Ren X, Wei H, Zhao L, Zhang X, Liu J, et al. INTRAVITREAL CONBERCEPT (KH902)
FOR SURGICAL TREATMENT OF SEVERE PROLIFERATIVE DIABETIC RETINOPATHY.  
Retina (Philadelphia, Pa). 2016;36(5):938-43.

18. Chen X, Li J, Li M, Zeng M, Li T, Xiao W, et al. KH902 suppresses high glucose-induced migration and sprouting of human retinal endothelial cells by blocking VEGF and PIGF. Diabetes, obesity & metabolism. 2013;15(3):224-33.

19. Bolz M, Ritter M, Schneider M, Simader C, Scholda C, Schmidt-Erfurth U. A systematic correlation of angiography and high-resolution optical coherence tomography in diabetic macular edema. Ophthalmology. 2009;116(1):66-72.

20. Barber AJ, Lieth E, Khin SA, Antonetti DA, Buchanan AG, Gardner TW. Neural apoptosis in the retina during experimental and human diabetes. Early onset and effect of insulin. The Journal of clinical investigation. 1998;102(4):783-91.

21. Byeon SH, Chu YK, Lee H, Lee SY, Kwon OW. Foveal ganglion cell layer damage in ischemic diabetic maculopathy: correlation of optical coherence tomographic and anatomic changes. Ophthalmology. 2009;116(10):1949-59 e8.

22. Tejerina AN, Vujosevic S, Varano M, Egan C, Sivaprasad S, Menon G, et al. One-year progression of diabetic subclinical macular edema in eyes with mild nonproliferative diabetic retinopathy: location of the increase in retinal thickness. Ophthalmic research. 2015;54(3):118-23.

23. Nguyen QD, Shah SM, Van Anden E, Sung JU, Vitale S, Campochiaro PA. Supplemental oxygen improves diabetic macular edema: a pilot study. Investigative ophthalmology & visual science. 2004;45(2):617-24.

24. Ebneter A, Wolf S, Abhishek J, Zinkernagel MS. RETINAL LAYER RESPONSE TO RANIBIZUMAB DURING TREATMENT OF DIABETIC MACULAR EDEMA: Thinner is Not Always Better. Retina (Philadelphia, Pa). 2016;36(7):1314-23.

25. Diabetic Retinopathy Clinical Research N, Wells JA, Glassman AR, Ayala AR, Jampol
LM, Aiello LP, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. The New England journal of medicine. 2015;372(13):1193-203.

26. Ray R, Stinnett SS, Jaffe GJ. Evaluation of image artifact produced by optical coherence tomography of retinal pathology. American journal of ophthalmology. 2005;139(1):18-29.

27. Lammer J, Scholda C, Prunte C, Benesch T, Schmidt-Erfurth U, Bolz M. Retinal thickness and volume measurements in diabetic macular edema: a comparison of four optical coherence tomography systems. Retina (Philadelphia, Pa). 2011;31(1):48-55.

Tables

Table 1. Overview of baseline demographic and clinical characteristics in our study

| Age       | Sex (Female)% | Injection times | Hypertension (%) | IOP (mmHg) |
|-----------|---------------|-----------------|------------------|------------|
| 60.55±8.65| 50.00         | 6.60±3.02       | 35.00            | 15.79±2.95 |

BCVA = Best Corrected Visual acuity; CRT = central retinal thickness; EDTRS = Early Treatment Diabetic Retinopathy Study; IOL = intraocular lens; IOP = intraocular pressure; MS = mean sensitivity of micrometry covering a 10°×10° area of macula.

Table 2. Correlation for BCVA Gain after One Year Conbercept Treatment and Individual Layer Thickness Changes from Different Regions.

| Region | RNFL Coefficient | GCL Coefficient | IPL Coefficient | INL Coefficient |
|--------|------------------|-----------------|-----------------|-----------------|
| Average| 0.389            | 0.415           | 0.473           | 0.411           |
| Central| 0.558            | 0.591           | 0.663           | 0.116           |
| I.S.   | 0.478            | 0.591           | 0.663           | 0.116           |
| I.I.   | 0.003            | 0.017           | 0.017           | 0.322           |
| I.N.   | 0.402            | 0.967           | 0.552           | 0.338           |
| I.T.   | 0.453            | 0.088           | 0.552           | 0.338           |
| O.S.   | 0.447            | 0.017           | 0.017           | 0.322           |
| O.I.   | 0.412            | 0.088           | 0.552           | 0.338           |
| O.N.   | 0.449            | 0.071           | 0.017           | 0.322           |
| O.T.   | 0.323            | 0.037           | 0.017           | 0.322           |

Significant p values are in bold.

Region: Standard EDTRS grid are used with central subfield (r = 0.5mm) (Central), inner...
ring (r=0.5-1.5mm) (I), outer ring (r=1.5-3mm) (O). Inner ring and outer ring are divided into four parts: superior part (S), inferior part (I), nasal part (N) and temporal part (T). I.S. stand for superior part of inner ring and so are the others.

Dependent variable: Best-corrected vision acuity (BCVA) gain at the Final Visit.

Explanatory variables: 1-year retinal nerve fiber layer thickness decrease (RNFL), 1-year ganglion cell layer thickness decrease (GCL), 1-year inner plexiform layer thickness decrease (IPL), 1-year inner nuclear layer thickness decrease (INL), 1-year outer plexiform layer thickness decrease (OPL), 1-year outer nuclear layer thickness decrease (ONL), 1-year photoreceptor-RPE-complex (PR) thickness decrease (external limiting membrane to Bruch’s membrane).

Table 3. Multivariate Regression Analysis of Factors with Influence on BCVA Gain after One Year Conbercept Treatment in Central Subfield

|                | Univariate Analysis (Pearson Correlation) | Multivariate Analysis (Adjusted R² = 0.544)* |
|----------------|------------------------------------------|-----------------------------------------------|
|                | Correlation Coefficient r | p       | Unstandardized Regression Coefficient B | Standardized Regression Coefficient β | p          |
| Constant       | 6.812                                    | <0.001  |                                    |                                     |
| BL BCVA        | 0.119                                    | 0.617   |                                    |                                     |
| IVTs           | -0.162                                   | 0.496   |                                    |                                     |
| RNFL           | 0.558                                    | 0.011   |                                    |                                     |
| GCL            | 0.591                                    | 0.006   | 1.752                              | 0.414                              | 0.022     |
| IPL            | 0.663                                    | 0.001   | 0.455                              | 0.523                              | 0.005     |
| INL            | 0.116                                    | 0.626   |                                    |                                     |
| OPL            | 0.458                                    | 0.042   |                                    |                                     |
| ONL            | 0.459                                    | 0.042   |                                    |                                     |
| PR             | 0.288                                    | 0.218   |                                    |                                     |

*Adjusted coefficient of multiple determination.

Significant p values are in bold.

Dependent variable: Best-corrected vision acuity (BCVA) gain at the Final Visit.

Explanatory variables: Baseline best-corrected visual acuity (BL BCVA), number of intravitreal injections (IVTs), 1-year retinal nerve fiber layer thickness decrease (RNFL), 1-year ganglion cell layer thickness decrease (GCL), 1-year inner plexiform layer thickness decrease (IPL), 1-year inner nuclear layer thickness decrease (INL), 1-year outer plexiform
layer thickness decrease (OPL), 1-year outer nuclear layer thickness decrease (ONL), 1-
year photoreceptor-RPE-complex (PR) thickness decrease (external limiting membrane to
Bruch’s membrane).

Table 4. Correlation for BCVA Gain after Three Conbercept Treatment and Mean Sensitivity
Changes from Different Regions.

| Region | Baseline(db) | 3months(db) | Changes(db) |
|--------|--------------|-------------|-------------|
| Average| 8.17±3.66    | 9.51±4.18   | 1.33±2.0    |
| Central| 4.60±2.95    | 5.87±3.68   | 1.27±2.3    |
| I.S.   | 8.59±3.92    | 9.86±4.34   | 1.28±1.6    |
| I.I.   | 8.79±4.54    | 10.56±4.81  | 1.78±2.6    |
| I.N.   | 9.80±4.92    | 11.15±4.76  | 1.35±1.7    |
| I.T.   | 9.09±4.19    | 10.09±4.85  | 1.00±2.2    |

Significant p values are in bold.

Region: Standard EDTRS grid are used with central subfield (r = 0.5mm) (Central), inner
ring(r=0.5-1.5mm) (I). Inner ring and outer ring are divided into four parts: superior
part(S), inferior part (I), nasal part (N) and temporal part (T). I.S. stand for superior part of
inner ring and so are the others.

Dependent variable: Best-corrected vision acuity (BCVA) gain at the Three months Visit.
Explanatory variables: changes of mean sensitivity in three months.

Figures
Figure 1

Individual layer thickness changes in study eye from baseline (BL) to one year of follow-up (A) Representative optical coherence tomogram scans showing layer
segmentation at baseline (BL) and at one-year (1-year) follow-up. Two-sided paired t-test was performed between baseline and month 12 (*p≤0.05; **p≤0.01; NS=not significant). Retinal layer thickness from BL to 12 months of continuous treatment in average changes (B), central subfield (C), and the inner superior region from inner ring (D) of the ETDRS grid. RNFL, retinal nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; PR, photoreceptor-RPE complex (Bruch membrane to external limiting membrane).

Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.

supplemental.docx