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Identifying the Prognostic Value of Non-Proliferative Diabetic Retinopathy Phenotypes in Response to Anti-VEGF Injection

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ABSTRACT

Background: Nonproliferative diabetic retinopathy [NPDR] is characterized by microvascular and intraretinal changes, including microaneurysms, hemorrhages, hard exudates, cotton wool spots, intraretinal microvascular abnormalities [IRMAs], and venous beadings.

The aim of the work: The Aim of this study is to evaluate the prognostic/predictive value of non-proliferative diabetic retinopathy phenotypes A, B and C in response to intravitreal Aflibercept injection for one year.

Patients and Methods: An interventional multi-arm prospective cohort study was performed to compare responses of different non-proliferative diabetic retinopathy NPDR phenotypes to intravitreal injections. Patients with mild to moderate NPDR were recruited and observed for 6 months, then allocated into three groups according to pattern of progression of diabetic retinopathy. Groups B and C received intravitreal injection on treat-and-extend basis. Results were collected and compared at the baseline visit, 6 months interval before receiving any treatment and 12 months from baseline visit [months after receiving the first dose].

Results: Comparing the ETDRS severity level according to the ETDRS severity scale, between the three groups shows statistically significant differences at all points of comparison. Concerning microaneurysms turnover. Groups B and C shows statistically significant changes among all visit concerning central foveal thickness, Group A shows no change in the mean central foveal thicknesses, while group B and C show statistically significant increase during the first 6 months of the study, and statistically significant decrease during the second 6 months of the study.

Conclusion: Anti-VEGF injection in NPDR without macular edema, is found useful in improving the DRSS and delaying or preventing the development of PDR. These results agree with data published by the PANORAMA clinical study.

Keywords: Anti-VEGF; NPDR; Nonproliferative; Diabetic; Retinopathy.

INTRODUCTION

Diabetes is one of the most prevalent non-communicable illnesses globally [1]. In Egypt, the majority of patients are on intensive insulin therapy, however poor glycemic control and microvascular complications are common [2].

Diabetic retinopathy [DR] is the specific microvascular complication of Diabetes Mellitus DM and affects 1 of 3 with DM. DR remains a leading cause of vision loss in working adult population. Patients with severe levels of DR are reported to have poor quality of life and reduced physical, emotional, and social well-being, and they utilize more health care resources [3].

Classically, nonproliferative diabetic retinopathy [NPDR] is characterized by micro-vascular and intraretinal changes, including microaneurysms, hemorrhages, hard exudates, cotton wool spots, intraretinal microvascular abnormalities [IRMAs], and venous beadings [4].

It is well recognized that the duration of diabetes and the level of metabolic control condition the development of the retinopathy, but these risk factors do not explain the great variability that characterizes the evolution and rate of progression of retinopathy in diabetic patients [5].

Mild NPDR in diabetes type 2 is further distinguished into three different phenotypes of disease progression to development of macular edema, the most frequent vision-threatening complication of DR [6].

Jose Cuhna-Vaz realized that by combining different imaging techniques, multimodal imaging of the macula made apparent three major patterns occurring. Pattern/Phenotype A included eyes with reversible and relatively little abnormal fluorescein leakage, a slow rate of microaneurysm formation and normal foveal avascular zone FAZ. This group appeared to represent eyes presenting slowly progressing retinal disease. Pattern/Phenotype B included eyes with persistently high leakage values, indicating important alteration in the blood retinal barrier BRB, high rate of microaneurysm accumulation and normal FAZ. All these features suggest a rapid and progressive form of the disease. This group may identify a 'Wet' form of diabetic retinopathy. Pattern/Phenotype C Included eyes with variable and reversible leakage and abnormal FAZ, this group may identify as 'ischemic' form of diabetic retinopathy [6].

PATIENTS AND METHODS

An interventional multi-arm prospective cohort study was performed to compare responses of different non-proliferative diabetic retinopathy NPDR phenotypes to intravitreal injections. Patients with mild to moderate NPDR were recruited and observed for 6 months, then allocated into three groups according to pattern of progression of diabetic retinopathy. Groups B and C received intravitreal injection on treat-and-extend basis. Results were collected and compared at the baseline visit, 6 months interval before receiving any treatment and 12 months from baseline visit [months after receiving the first dose]. Groups: Group A: NPDR Phenotype A. Group B: NPDR Phenotype B. Group C: NPDR Phenotype C.

Inclusion Criteria for recruitment: Type 2 Diabetes > 5 years, Showing any sign of diabetic retinopathy [single microaneurysm is a bottom-line], didn't receive any intravitreal injection. Exclusion criteria from recruitment: Significant media opacity [Cornea, Cataract, vitreous opacity], previous complicated cataract surgery, receiving any treatment for diabetic retinopathy [Intravitreal injection or laser].

Inclusion Criteria for Group A: Type 2 diabetes > 5 years, Mild NPDR, Microaneurysm turnover < 6, Central foveal thickness < 275 microns in males, 260 microns in females.

Exclusion criteria for group A: Developing PDR, Receiving any undocumented treatment for diabetic retinopathy during the follow-up period, developing any media opacity that prevents acquisition of useful retinal images, developing any other retinal comorbidities.

Inclusion Criteria for Group B: Type 2 diabetes > 5 years, Mild to Moderate NPDR, Microaneurysm turnover < 6, Central foveal thickness > 275 microns for males, 260 microns for females.

Exclusion criteria for Group B: Developing PDR, receiving any undocumented treatment for diabetic retinopathy during the follow-up period, developing any media opacity that prevents acquisition of useful retinal images, developing any other retinal comorbidities.

Inclusion Criteria for Group C: Type 2 diabetes > 5 years, any form of NPDR, Micro-aneurysm turnover > 6, any central foveal thickness.

Exclusion Criteria for Group C: Receiving any undocumented treatment for diabetic retinopathy during the follow-up period, developing any media opacity that prevents acquisition of useful retinal images, developing any other retinal comorbidities.

General examination was performed to check the general condition of the patient and exclude any other systemic or metabolic disease, laboratory work up included HbA1c, FBS and lipid profile.

Full ophthalmic examination to check for uncorrected visual acuity UCVA and best corrected visual acuity BCVA using LogMAR chart. Pupil reaction, slit lamp examination of the anterior and posterior chambers, intraocular pressure assessment using Goldman applanation tonometer.

Colored fundoscopscopic images and OCT. Microaneurysms were counted manually using CountThings App by Dynamic Ventures, Inc, A software company based in Cupertino, California.

The software allows upload of an image, with manual marking of specific objects in the image, then a counter automatically calculates the sum of all objects marked. Each image was processed for four times and an average number of micro-aneurysm is calculated. Microaneurysms get sometimes confused with intraretinal hemorrhages, so unless an intraretinal hemorrhage is morphologically distinctable from micro-aneurysms, it couldn't be ruled out.

After allocation of participants into three phenotype-based groups A, B and C. groups B and started to receive intravitreal injections on treat-and-extend basis. Every patient in group B and C received a loading dose of three injections with one month apart, each is 2mg. Then the interval got extended by 2 weeks until the end of the study. Each patient received 5 injections by the end of the study. Intravitreal injection is done routinely through the pars plana 3.5-4.0 mm away from the limbus with a paracentesis performed at the end of the injection, in a completely aseptic environment. Images were acquired one more time at the end of the study, to analyze the effect of intravitreal injection, and compare with baseline and 6-month interval images.

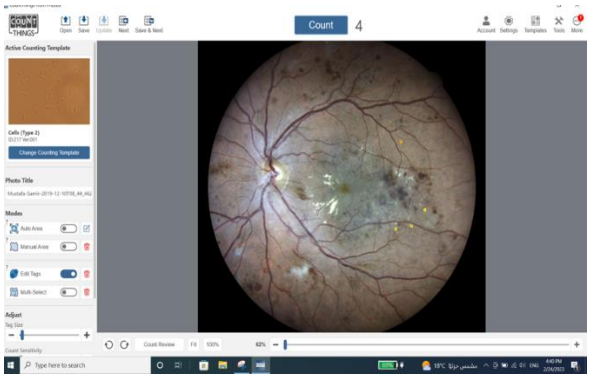

Figure [1]: CounThings user interface, with the image processed for analysis appear on the center, yellow dots on the image show manual marking

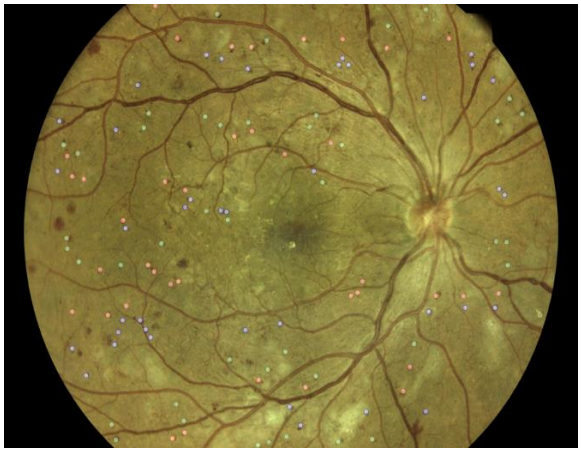

Figure [2]: A processed image appear, microaneurysms appear marked manually with dots. An automated counter appears on the upper right side of the image.

Statistical analysis

Statistical analysis was performed with SPSS statistical software, version 25 [IBM, Chicago, Illinois, USA]. The normality of the data was tested by the Kolmogorov-Smirnov test. Qualitative data were presented as numbers and percentages and the comparison between the 3 groups were done using the Chi square test, while quantitative data were presented as mean and standard deviations and median and interquartile range, and the comparison between the three study-groups was done by one way ANOVA test. Pairwise comparison bet. Each 2 groups was done using Post Hoc Test [Tukey]. As a result, the p-value was considered significant at the level of <0.05.

RESULTS

Statistical analysis shows no statistically significant differences in gender distribution into the three groups, age of participants or in duration of diabetes. HbA1c value doesn't show a statistically significant value between groups A and B or B and C, however comparing group A to C shows a statistically significant difference

p= 0.018 as appears in Table 1 value p2, this finding supports the thesis that HbA1c is a biomarker since the group that showed that statistically significant difference will show the least response to intravitreal injection.

During the second and third visits all patients show a value for HbA1c that show no statistically significant differences when compared. Table 2 compares the value of HbA1c in each group separately, group by and c shows significant drop of the HbA1c value when the last visit is compared the first visit.

Figure 3 illustrates the progress of HbA1c along the course of the study, Group-A showed minimal worsening that wasn't statistically significant, while group B and C shows a drop in the value which means statistically significant improvement. The drop in HbA1c in all groups wasn't directly proportional with progress of diabetic retinopathy.

Comparing the ETDRS severity level according to the ETDRS severity scale, between the three groups shows statistically significant differences at all points of comparison. ETDRS severity level showed almost linear progress throughout the course of the study in Group A, in Groups B and C it showed a statistically significant increase during the follow up period of 6 month, in group B the mean average increased from 34.65 ± 3.83 to 43.80 ± 2.26, by the end of the study after 1 year of the baselines visit, the mean value regressed to 20.50 ± 4.05 that was significantly lower than the severity level of the baseline value. DR severity level in group C showed the highest increase during the first 6 months, with a mean average progressed from 36.80 ± 3.73 to 54.20 ± 5.38. Mean severity level in group C decreased to 47.05 ± 7.69 by the end of the study, a value that's higher than the baseline value, unlike group B that showed a lower value than the baseline value by the end of the study. Figure 4 illustrates this relationship.

Microaneurysm count MA shows no statistically significant difference between the first and second visit for group A p1 however by the end of the year, there's an increase of the mean number p2 from 11.83 ± 4.19 to 13.05 ± 4.21 Table 3.

Groups B and C showed statistically significant changes among all visit with the second visit show significant increases in the mean averages 110.3 ± 39.89, 324.8 ± 115.3 in groups B and C respectively, then decrease at the end of the study to 54.23 ± 16.41 and 198.9 ± 102.0.

Table 4 compares central foveal thickness in each group separately during the first, second and third visits. Group A shows no change in the mean central foveal thicknesses, while group B shows significant increase after 6 months of the baselines with the mean average increased from 283.5 ± 12.64 to 334.8 ± 41.48, after receiving intravitreal injection, mean thickness regressed to 274.6 ± 28.12 that's lower than the average baseline value of the same group. Group C showed a statistically significant increase of the mean thickness from 273.5 ± 29.48 to 372.5 ± 60.39, and significant decrease after receiving intravitreal injection to 253.8 ± 23.62. Mean thickness of group C showed better improvement than group B after receiving the same dose of intravitreal injection, however severity scale remained higher. Comparing BCVA among the three groups showed better improvement in group C, from 0.24 ± 0.12 at 6 months to 0.67 ± 0.11 after 1 year.

Table [1]: Comparison between the three studied groups according to HbA1C

	HbA1C	Group A [n = 20]	Group B [n = 20]	Group C [n = 20]	F	p
Baseline	**Min. – Max.**	6.0 – 8.30	6.70 – 9.50	5.90 – 12.0	4.294*	0.018*
	Mean ± SD.	7.26 ± 0.67	7.73 ± 0.61	8.19 ± 1.48		
	Median [IQR]	7.25 [6.75 – 7.85]	7.60 [7.40 – 8.05]	8.25 [7.05 – 9.05]		
	Sig. bet. grps.	p_1=0.315,p_2=0.013*,p_3=0.315				
6 months	**Min. – Max.**	6.10 – 8.60	6.10 – 9.0	6.10 – 9.90	0.996	0.376
	Mean ± SD.	7.36 ± 0.84	7.29 ± 0.62	7.66 ± 1.11		
	Median [IQR]	7.25 [6.55 – 8.10]	7.30 [6.95 – 7.60]	7.45 [7.0 – 8.25]		
1 year	**Min. – Max.**	5.90 – 11.0	5.90 – 8.0	6.10 – 11.0	2.392	0.101
	Mean ± SD.	7.49 ± 1.31	6.82 ± 0.57	7.40 ± 1.14		
	Median [IQR]	7.30 [6.40 – 8.25]	6.90 [6.45 – 7.10]	7.15 [6.60 – 7.90]		

IQR: Inter quartile range. SD: Standard deviation. F: One way ANOVA test. p: p value for comparing between the three studied groups. p_1: p value for comparing between Group A and Group B. p_2: p value for comparing between Group A and Group C. p_3: p value for comparing between Group B and Group C. *: Statistically significant at $p \leq 0.05$

Table [2]: Comparison between the three studied periods according to HbA1C

	HbA1C	Baseline	6 months	1 year	F	p
Group A [n=20]	Min. – Max.	6.0 – 8.30	6.10 – 8.60	5.90 – 11.0	1.019	0.334
	Mean ± SD.	7.26 ± 0.67	7.36 ± 0.84	7.49 ± 1.31		
	Median [IQR]	7.25 [6.75 – 7.85]	7.25 [6.55 – 8.10]	7.30 [6.40 – 8.25]		
Group B [n=20]	Min. – Max.	6.70 – 9.50	6.10 – 9.0	5.90 – 8.0	25.389*	<0.001*
	Mean ± SD.	7.73 ± 0.61	7.29 ± 0.62	6.82 ± 0.57		
	Median [IQR]	7.60 [7.40 – 8.05]	7.30 [6.95 – 7.60]	6.90 [6.45 – 7.10]		
	Sig. bet. periods	p_1=0.007*,p_2<0.001*,p_3=0.007*				
Group C [n=20]	Min. – Max.	5.90 – 12.0	6.10 – 9.90	6.10 – 11.0	5.471*	0.027*
	Mean ± SD.	8.19 ± 1.48	7.66 ± 1.11	7.40 ± 1.14		
	Median [IQR]	8.25 [7.05 – 9.05]	7.45 [7.0 – 8.25]	7.15 [6.60 – 7.90]		
	Sig. bet. periods	p_1=0.011*,p_2=0.089,p_3=0.619				

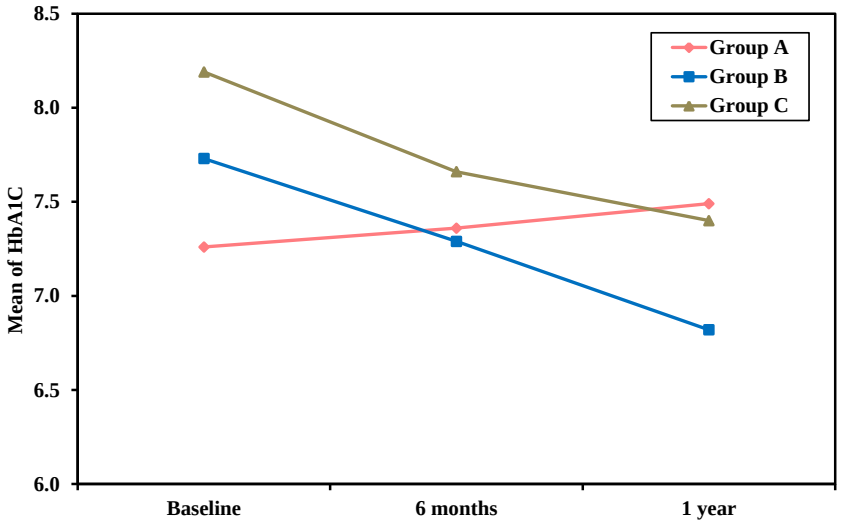

Figure 1 Comparison between the three studied periods according to HbA1C

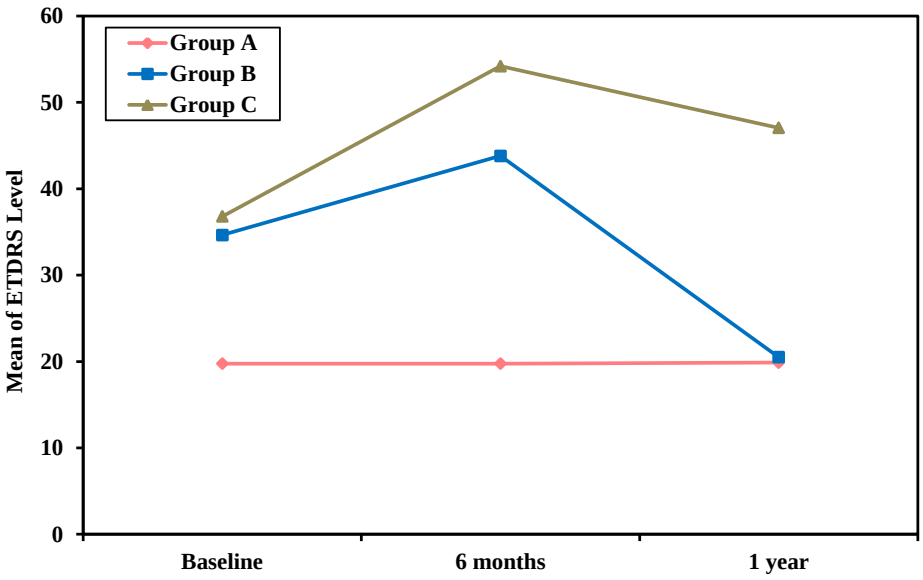

Figure 2 Comparison between the three studied periods according to ETDRS Level

Table [3]: Comparison between the three studied periods according to MA

MA	Baseline	6 months	1 year	Fr	p
Group A [n = 40]					
Min. – Max.	4.0 – 21.0	5.0 – 24.0	7.0 – 23.0	**25.824***	**<0.001***
Mean ± SD.	11.73 ± 4.51	11.83 ± 4.19	13.05 ± 4.21		
Median [IQR]	10.50 [8.50 – 16.0]	11.0 [9.0 – 14.0]	13.0 [10.0 – 15.0]		
Sig. bet. periods	**p_1=0.502,p_2<0.001*,p_3<0.001***				
Group B [n = 40]					
Min. – Max.	10.0 – 50.0	42.0 – 201.0	26.0 – 82.0	**74.150***	**<0.001***
Mean ± SD.	29.63 ± 10.62	110.3 ± 39.89	54.23 ± 16.41		
Median [IQR]	28.50 [21.0 – 38.5]	108.0[84.50 – 137.0]	56.0 [39.0 – 67.50]		
Sig. bet. periods	**p_1<0.001*,p_2<0.001*,p_3<0.001***				
Group C [n = 40]					
Min. – Max.	17.0 – 101.0	102.0 – 606.0	60.0 – 503.0	**80.00***	**<0.001***
Mean ± SD.	50.85 ± 19.46	324.8 ± 115.3	198.9 ± 102.0		
Median [IQR]	46.50[38.50 – 60.5]	300.0[263.0 – 390.5]	194.0[123.0 – 258.0]		
Sig. bet. periods	**p_1<0.001*,p_2<0.001*,p_3<0.001***				

Table [4]: Comparison between the three studied periods according to CFT

CFT	Baseline	6 months	1 year	F	p
Group A [n = 40]					
Min. – Max.	206.0 – 230.0	206.0 – 230.0	206.0 – 230.0	–	–
Mean ± SD.	223.0 ± 5.38	223.0 ± 5.38	223.0 ± 5.38		
Median [IQR]	224.0 [221.0 – 226.0]	224.0 [221.0 – 226.0]	224.0 [221.0 – 226.0]		
Group B [n = 40]					
Min. – Max.	255.0 – 310.0	270.0 – 450.0	230.0 – 357.0	**80.772***	**<0.001***
Mean ± SD.	283.5 ± 12.64	334.8 ± 41.48	274.6 ± 28.12		
Median [IQR]	287.0 [275.0 – 290.0]	330.0 [300.0 – 356.0]	266.0 [251.5 – 298.5]		
Sig. bet. periods	p_1<0.001*,p_2=0.125,p_3<0.001*				
Group C [n = 40]					
Min. – Max.	235.0 – 350.0	260.0 – 549.0	225.0 – 301.0	**171.04***	**<0.001***
Mean ± SD.	273.5 ± 29.48	372.5 ± 60.39	253.8 ± 23.62		
Median [IQR]	273.5 [247.5 – 295.0]	372.5 [347.5 – 400.0]	245.0 [233.0 – 272.5]		
Sig. bet. periods	p_1<0.001*,p_2<0.001*,p_3<0.001*				

DISCUSSION

A 1-year study of patients with type II diabetes presenting with mild to moderate non-proliferative diabetic retinopathy confirms that there're different patterns of development of the disease irrelevant to general condition of patients and to some extent diabetic control, namely diabetic retinopathy phenotypes. Different diabetic retinopathy phenotypes also showed different responses to the same treatment protocol with intergroup consensus, which confirms the interpretive ability of the phenotype theory.

We noted in our study that ETDRS level 35 is considered a turning point for phenotypes B and C, that phenotype C is mainly identified at ETDRS level 35. Eyes with ETDRS level 35 apparently reach a status of microvascular damage that creates the condition for either stabilization or progression demonstrated by identification of Phenotype C. In November 2022 Hatano M and associates from Japan published a study to evaluate microaneurysms as predictors of therapeutic response to anti-VEGF therapy in patients with DME [7].

Another study comes from Japan by Mori K and associates published in January 2020, focusing only on number of microaneurysms in response to intravitreal anti-VEGF injection. Mori denotes that since MAs present around occluded capillaries that exhibit loss of cellular components from which VEGF is produced, there seems to be an association between MAs and angiogenesis, suggesting a link between MAs and VEGF [8].

In our study we found a decrease in MAs number as well as microaneurysm turnover, when we compared the relationship between MAT1/MAT2 and MAT3/MAT in groups B and

C this shows a direct response in microaneurysm number to intravitreal anti-VEGF injection.

Of great significance, is also the effect of intravitreal Anti-VEGF injection on diabetic retinopathy severity level we demonstrated in our study. NPDR phenotypes are apparently related DRSS and the speed of developing into more advanced steps on the scale. Eyes with NPDR allocated in phenotype-A group were showing a DRSS of 15-20 and didn't show any progress during the course of the study. Whilst in phenotype B group the median baseline DRSS level was 35 and showed 1 step progress during the first 6 months, without receiving any treatment, on the other hand, eyes with phenotype C NPDR showed 3-step progress at the same time interval as a median value from 35 to 53. After receiving the loading dose of three-monthly injections of anti-VEGF and two following doses, the median DRSS level for phenotype B group regressed 2 steps back compared to the 6 months value, and for phenotype C regressed 1-step back. Our results are compatible with the results from the PANORAMA randomized clinical trial [9].

The PANORAMA clinical trial was published in August 2021 and was aiming at evaluation of vascular endothelial growth factor blockade therapy with intravitreal aflibercept injections with eyes with severe NPDR without diabetic macular edema. Treatment of severe NPDR with intravitreal aflibercept injections in the PANORAMA clinical trial improved the severity of retinopathy and reduced the risk of progression of CIMA and VTC vs sham treatment with observation.

Conclusion: Cases allocated in phenotype B group showed better response to intra-vitreal anti-VEGF injection with better improvement of macular edema, BCVA with more than 2 step improvement on the diabetic retinopathy severity scale, while cases in phenotype C showed less improvement in macular edema, BCVA with only one step improvement on the diabetic retinopathy severity scale. Cases allocated in phenotype A-group didn't show any VTDC during the whole course of the study, with no clinically significant changes in microaneurysm count or center retinal thickness.

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