

Ranibizumab versus aflibercept for macular edema secondary to nonischemic central retinal vein occlusion in young adult patients

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Research Article

Keywords: Aflibercept, intravitreal injection, non-ischemic CRVO, Ranibizumab

Posted Date: March 30th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1490565/v1>

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Abstract

Purpose

to compare effect Ranibizumab and Aflibercept, for the treatment of macular edema secondary to non-ischemic central retinal vein occlusion CRVO in young adults.

Methods

Forty eyes of 40 young adult patients with macular edema due to CRVO were enrolled in this prospective double-armed clinical trial. The patients were randomized into 2 groups of 20 patients each. First group received intravitreal injection of Ranibizumab while second group received Aflibercept. All patients were subjected to measurement of Best corrected visual acuity BCVA, fluorescein angiography (FA) to detect retinal ischemia and Spectral domain OCT (SD-OCT) to measure macular edema at baseline and during 12-month follow up period. Intravitreal injections were three injections with a 1-month interval between injections.

Results

BCVA in group 1 had significant steady increase over time from baseline to 1 year [55.9 ± 10.3], $p = 0.017$). Group 2 had also significant steady increase over time from baseline to 1 year [60.8 ± 8.4], $p = 0.035$) with no significant difference between the 2 groups ($p > 0.05$). Regarding central subfield thickness CST, in the first group, statistically significant decrease in the CST over time from baseline to 1 year [$295.1 \pm 56 \text{ Um}$], $p < 0.001$). similar results in the second group from the baseline to 1 year [$328.2 \pm 72 \text{ Um}$] with no statistically significant difference ($p > 0.05$).

Conclusion

Ranibizumab and aflibercept showed a comparable promising outcome in the management of macular edema secondary to nonischemic CRVO in patients aged < 50 years.

Trial registration number : NCT05282420

Key Messages

- This study was conducted to patients younger than 50 years old with macular edema secondary to non-ischemic CRVO to detect the effect of the two FDA approved anti-VEGF drugs i.e., Ranibizumab and Aflibercept on vision and retinal (macular) edema in such age group with non-ischemic CRVO.
- The study found that the two drugs had comparable outcome regarding the final functional outcome i.e. vision and the anatomical outcome i.e. reduction of the macular edema.

Introduction

Central retinal vein occlusion (CRVO) is the second most common visually disabling retinal vascular disorder after diabetic retinopathy (1). Depending on the amount of retinal ischemia, retinal vein occlusions (RVOs) have been divided into ischemic and nonischemic types (2, 3) (4). The prevalence of RVO increases with age (3, 5). The occurrence of CRVO in adults under 50 years old is considerably less common than that in older patients (6). Other CRVO studies have reported a prevalence between 10% and 25% in patients aged ≤ 50 years (7). CRVO results from central retinal vein obstruction, leading to increased pressure, reduced arterial perfusion, and retinal ischemia. Retinal ischemia induces vascular endothelial growth factor (VEGF) production that may subsequently promote vascular permeability, macular edema, retinal hemorrhages, capillary non-perfusion, and/or neovascularization. Therefore, anti-VEGF medications become an important drug target in ophthalmology (8, 9). VEGF inhibition by intravitreal medications (ranibizumab [LUCENTIS; Genentech, South San Francisco, CA], bevacizumab [Avastin; Genentech, South San Francisco, CA], and aflibercept [EYLEA; Regeneron Pharmaceuticals, Tarrytown, NY]) and intravitreal corticosteroids are effective for the treatment of macular edema associated with CRVOs. Only ranibizumab and aflibercept obtained Food and Drug Administration (FDA) approval for the treatment of macular edema secondary to CRVO (10, 11). However, there are few (12, 13) comparative studies evaluating the two approved anti-VEGF agents in terms of anatomical and functional results in treatment-naïve patients with macular edema secondary to CRVO. Moreover, no comparative studies in patients with nonischemic CRVO aged < 50 years are available. Therefore, this study aimed to compare the efficacy and safety of two anti-VEGF agents, ranibizumab and aflibercept, for the treatment of macular edema secondary to CRVO in young adult patients below 50 years old over a 12-month follow-up period.

Patients And Methods

A total of 40 eyes of 40 patients aged < 50 years with macular edema secondary to nonischemic CRVO were enrolled in this prospective double-armed randomized interventional study. All patients were treatment-naïve.

The study was conducted after obtaining approval from the Institutional Ethics Committee in accordance with the Declaration of Helsinki and the Medical Research Council's Guidelines for Ethical Biomedical Research on Human Subjects. All participants provided written informed consent prior to enrollment in the study.

The patients were randomized into 2 groups of 20 patients (20 eyes). The first and second groups received 0.5 mg of ranibizumab intravitreal injections and 2.0 mg of aflibercept intravitreal injections, respectively. All patients were followed up for at least 12 months.

The planned treatment was employed on all patients throughout the study, and no switching was performed between anti-VEGF drugs.

Exclusion criteria

Patients with other conditions that may affect the macula, including diabetic retinopathy, intraocular inflammation, age-related macular degeneration, solar or radiation retinopathy, ischemic-type CRVO, and recent intraocular surgery, were excluded from the study. Furthermore, we excluded patients who had previous intravitreal injections, who had ophthalmic laser surgeries, and with dense cataracts whom the fundus was difficult to scan. Patients who were lost to follow-up were also excluded.

All patients initially received three loading doses of intravitreal injections of either 0.5 mg of ranibizumab (first group) or 2.0 mg of aflibercept (second group), with a 1-month interval between injections. After the three initial injections, patients received additional *pro re nata* (PRN) injections whenever indicated. The indications of PRN injections were as follows: a decrease in BCVA of one or more lines on the Snellen chart, an increase in central subfield thickness of ≥ 50 μm , or an OCT evidence of intraretinal or subretinal fluid. Patients who showed neovascularization in the fundus were listed for panretinal photocoagulation. All patients underwent the same protocol of intravitreal injection and retinal laser.

The sterile protocol for intravitreal injection included the use of 5% povidone-iodine solution, topical anesthesia, eyelid speculum application, and intravitreal injection of the medication via the pars plana in the inferotemporal quadrant 4 mm from the limbus in phakic eyes and 3.5 mm in pseudophakic eyes, followed by postoperative topical antibiotic eye drops.

All patients underwent clinic-based BCVA measurement at each visit. Spectral domain OCT (SD-OCT) and fluorescein angiography (FA) were performed at baseline using the SPECTRALIS HRA + OCT (Heidelberg Engineering, Heidelberg, Germany) to determine the type of CRVO (ischemic or nonischemic). SD-OCT was performed monthly thereafter. Retinal ischemia was assessed using FA every 3 months or earlier at the physician's discretion. This study excluded eyes with ischemic-type CRVO, which was defined as an area of retinal non-perfusion > 10 disc diameters, which could involve the periphery and/or the macula. Macular ischemia was defined as follows: (1) foveal avascular zone (FAZ) $> 1,000$ μm and (2) broken perifoveal capillary rings at the FAZ borders, with distinct capillary non-perfusion areas within one disc diameter of the foveal center in the transit phase of FA. Furthermore, the ellipsoid zone status and macular edema type (cystoid or diffuse) were recorded at each visit. The total number of injections was also recorded. The primary outcomes included the mean change in BCVA and CST from baseline and the percentage of patients with resolution of edema (no SRF/IRF at the macula) at 12 months. In this study, the response toward each intravitreal drug injected and the factors affecting the response were examined.

Statistical analysis

Data were verified, coded by the researcher, and analyzed using IBM-SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA)*. Descriptive statistics: means, standard deviations, medians, ranges, and percentages were calculated. Test of significances: Chi-square/Fisher's exact/Monte Carlo exact test was calculated to compare the frequencies among groups. Independent t-test analysis was performed to compare the means of dichotomous data. For continuous variables with more than two categories on repeated measures, two-way repeated measures analysis of variance test was calculated to test the mean

differences of data with normal distribution and have repeated measures (between-group, within-group, and overall differences). P values ≤ 0.05 were considered statistically significant.

Results

The sociodemographic characteristics of the studied sample according to the treatment groups are presented in Table 1. No statistically significant difference in the mean age between the two groups was observed ($p = 0.202$). Moreover, sex distribution was matched (female/male = 2/18). Similarly, nonsignificant differences in the rate of past history of the main chronic diseases were noted in both groups ($p > 0.05$). Treatment duration before study initiation showed nonsignificant differences ($p = 0.705$).

The effect of treatment modalities on the visual parameters over the study period is shown in Table 2. For group 1 (**ranibizumab group**), a significant steady increase in BCVA over time from baseline to 1 year was noted (at baseline $[48.3 \pm 6.4]$, 6 months $[53.5 \pm 7.2]$, and 12 months $[55.9 \pm 10.3]$, $p = 0.017$). Similarly, in group 2 (**aflibercept group**), BCVA showed a significant improvement over the study period (at baseline $[55.9 \pm 7.2]$, 6 months $[57.3 \pm 5.7]$, and 12 months $[60.8 \pm 8.4]$, $p = 0.035$). Moreover, no statistically significant differences between the two groups over the study period were observed ($p > 0.05$). For the interaction between time and treatment, significantly better results regarding BCVA were noted in the **aflibercept group** over time ($p < 0.001$).

Regarding CST, in group 1 (**ranibizumab group**), a statistically significant decrease in the CST over time from baseline to 1 year was noted (at baseline $[557.9 \pm 69 \text{ Um}]$, 6 months $[398.4 \pm 69 \text{ Um}]$, and 12 months $[295.1 \pm 56 \text{ Um}]$, $p < 0.001$). Figure 1 shows an example. In addition, in group 2 (**aflibercept group**), CST showed a significant reduction over time (at baseline $[570.7 \pm 59 \text{ Um}]$, 6 months $[388.5 \pm 80 \text{ Um}]$, and 12 months $[328.2 \pm 72 \text{ Um}]$, $p < 0.001$). Figure 2 shows an example. Moreover, the mean CST difference between the two groups was not statistically significant for each study period ($p > 0.05$). The interaction between time and treatment did not reveal significant differences ($p = 0.497$) (Table 2).

In group 1, the percentage of patients with resolved macular edema significantly increased from 5% at 6 months to 40% at 12 months ($p = 0.032$). Similarly, in group 2, cases with resolved macular edema significantly increased from 20% at 6 months to 50% at 12 months ($p = 0.024$). However, at 6 and 12 months, group 2 showed a higher proportion of resolved cases, although this was not statistically significant ($p = 0.066$ and 0.709 , respectively) (Table 3).

The treatment outcome is presented in Table 4. The proportion of patients with disrupted ellipsoid zones at the end of the study in the ranibizumab group was double (10%) compared with that in the aflibercept group (5%) ($p = 1.000$). Furthermore, an almost equal proportion of patients in both groups needed further injection (50% vs. 45%) ($p = 0.807$). An insignificantly higher mean number of injections were recorded at the end of the study in group 1 (5.4 ± 0.8) than those in group 2 (4.9 ± 1.2) ($p = 0.314$).

Table 1
Baseline characteristics of the studied cohort

	Group I (n = 20)	Group II (n = 20)	P-value
Age/years	43.65 ± 4.6	45.40 ± 3.9	= 0.202*
Sex (male/female)	18/2	18/2	= 1.000**
Past history			
• None	8 (40%)	8 (40%)	
• Diabetes mellitus DM	3 (15%)	7 (35%)	= 0.589***
• Hypertension HTN	4 (20%)	3 (15%)	
• Hyperlipidemia	2 (10%)	1 (5%)	
• Glaucoma	3 (15%)	1 (5%)	
DD before treatment			= 0.705**
• < 3 months	15 (75%)	16 (80%)	
• > 3 months	5 (25%)	4 (20%)	

*Independent t-test was used to compare the means among groups

**Chi-square analysis was used to compare the frequency among groups

***Monte Carlo exact test was used to compare the frequency among groups

Table 2
Effects of treatment modalities on the visual parameters over time

(Mean ± SD)	Group I (n = 20)	P-value**	Group II (n = 20)	P-value**	P-value*
BCV					
• Baseline	48.25 ± 6.4	= 0.008	55.90 ± 7.2	= 0.296	= 0.001
• 6 months	53.50 ± 7.2	= 0.134	57.25 ± 5.7	= 0.021	= 0.077
• 12 months	55.85 ± 10.3	= 0.005	60.75 ± 8.4	= 0.011	= 0.109
P-value*	= 0.017		= 0.035		P = 0.010***
CST					
• Baseline	557.85 ± 69.7	< 0.001	570.65 ± 59.2	< 0.001	= 0.537
• 6 months	398.35 ± 69.1	< 0.001	388.50 ± 80.1	= 0.001	= 0.681
• 12 months	295.10 ± 55.9	< 0.001	328.20 ± 72.4	< 0.001	= 0.114
P-value*	< 0.001		< 0.001		P = 0.497***

*Mean differences between-group and within-group comparison

**Post hoc test was used for pairwise comparison with Bonferroni correction

***Two-way repeated measures analysis of variance was used to compare the mean differences over time

Table 3
Effects of treatment modalities on the macular edema type over time

	Group I (n = 20)	Group II (n = 20)	P-value*
At 6 months			
• Cystoid	12 (60%)	5 (25%)	= 0.066
• Diffuse	7 (35%)	11 (55%)	
• Resolved	1 (5%)	4 (20%)	
At 12 months			
• Cystoid	8 (40%)	5 (25%)	= 0.709
• Diffuse	4 (20%)	5 (25%)	
• Resolved	8 (40%)	10 (50%)	
P-value**	= 0.032	= 0.024	

*Chi-square analysis was used to compare the frequency among groups

**McNemar test was used to compare the frequency over time within groups

Table 4
Outcome results of the treatment groups

	Group I (n = 20)	Group II (n = 20)	P-value
Disrupted ellipsoid zone at the end of the study			
	2 (10%)	1 (5%)	= 1.000*
Need for further injection			
• None	8 (40%)	10 (50%)	= 0.807**
• Yes	10 (50%)	9 (45%)	
• Discontinued	2 (10%)	1 (5%)	
Total no. of injections at the end of the study			= 0.314***
• Mean \pm SD	5.40 \pm 0.8	4.90 \pm 1.2	
• Median (range)	5.5 (3–6)	5 (3–6)	

*Fisher's exact test was used to compare the frequency among groups

**Monte Carlo exact test was used to compare the frequency among groups

***Independent t-test was used to compare the means among groups

Discussion

Several treatment options have been advocated for the management of macular edema secondary to CRVO, including grid laser photocoagulation and intravitreal injections of corticosteroids and anti-VEGF molecules (14–20). However, RVO in patients aged < 50 years has been poorly investigated.

To date, only two previous studies have addressed the management of macular edema secondary to CRVO in patients aged < 50 years, the first of which concluded that dexamethasone implants could offer significant improvements in half of the patients after a 12-month follow-up. However, dexamethasone drawbacks were evident in approximately one third of the patients who developed intraocular pressure elevation as a treatment complication (18). The other more recent study has adopted intravitreal injection with anti-VEGF (21). The authors investigated the effectiveness of ranibizumab for the management of ME, with no exclusion of cases with ischemic-type CRVO. To our knowledge, this is the first study to assess the effect of intravitreal anti-VEGF injection in patients aged < 50 years with selectively nonischemic CRVO. Furthermore, this study is the first to compare the two approved anti-VEGF injections in such patient categories. This study demonstrated a significant steady elevation of BCVA and reduction of CST from baseline to 12 months.

In our study, the change in BCVA over the study period was approximately + 7.6 and + 4.85 letters in the ranibizumab and aflibercept groups, respectively. Consistent with our findings, the study by Chatziralli et al. (2017) found that ranibizumab was superior to aflibercept in the management of CRVO and showed a higher change in BCVA (20). However, although the authors included cases aged > 50 years and those with ischemic CRVO, our figures of improvement were inferior to their reported figures; they found that the change in BCVA from baseline to 12 months was approximately + 9.0 and + 8.3 letters in the ranibizumab and aflibercept groups, respectively. This may be attributed to their higher baseline figures as their study patients started with mean BCVA values of 66.2 and 61.3 letters compared with 48.3 and 55.9 letters in the present study. When expressing the improvement in terms of percentages, the percentages of improvement were 13.6% and 13.5% in their study compared with 15.7% and 8.7% in ours for the ranibizumab and aflibercept groups, respectively. The worse aflibercept efficacy in our cohort is consistent with that of Lehmann-Clarke et al. (2015) who reported that aflibercept yields better outcomes in ischemic cases (22).

In patients aged < 50 years, Battaglia Parodi et al. (2020) (21) reported approximately 23% BCVA improvement after 1-year ranibizumab treatment. Their superior outcome may be related to the higher number of injection times as they injected their patients up to nine times during the study, whereas in the present study, the maximum number of injection times was six. At the end of the follow-up period, it was found that 40% and 50% of the patients showed macular edema resolution in the ranibizumab and aflibercept groups, respectively. This is comparable to the study of Battaglia Parodi et al. (2020) (21) who found a macular edema resolution rate of 63% when using ranibizumab and Chatziralli et al. (2017) (20)

who reported macular edema resolution rates of 55.9% and 50% in the ranibizumab and aflibercept groups, respectively, after a similar period. This may be related to the higher number of injection times since Chatziralli et al. (2017) (20) reported mean values for injection times of 6.8 ± 1.3 and 6.1 ± 2.0 for the two groups compared with 5.40 ± 0.8 and 4.90 ± 1.2 in the present study.

Of note, in this study, both treatment arms did not show significant differences concerning BCVA improvement, CST reduction, macular edema resolution, ellipsoid zone disruption, or the needed injections over the follow-up period. This is consistent with the findings of Chatziralli et al. (2017) (20) and the earlier study conducted by the Diabetic Retinopathy Clinical Research Network (2015) (23) who reported comparable effectiveness of intravitreal aflibercept and ranibizumab in the treatment of diabetic macular edema.

Our finding is consistent with what was previously presumed that the VEGF load found in RVO is highly exceeding that of diabetic retinopathy or age-related macular degeneration (24), and thus, such greater VEGF load may overcome the variations in the anti-VEGF types (20).

This study has some limitations. It is limited by the absence of a control group, the short follow-up period, and the relatively small sample size, which was attributed to the relative difficulty in including patients aged < 50 years. However, the study is strengthened by its prospective design, selecting a particular category of patients and comparing two FDA-approved treatments.

Conclusion: Ranibizumab and aflibercept showed a comparable promising outcome in the management of macular edema secondary to nonischemic CRVO in patients aged < 50 years.

Declarations

The study was conducted after the approval of regional research ethics committee.

Informed consent was obtained from all individual participants included in the study.

The study data is available upon the request of the editor.

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

All authors declare that there is no conflict of interest.

Source(s) of funding: None.

All authors contributed equally in this work.

The article has not been presented in a meeting.

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Figures

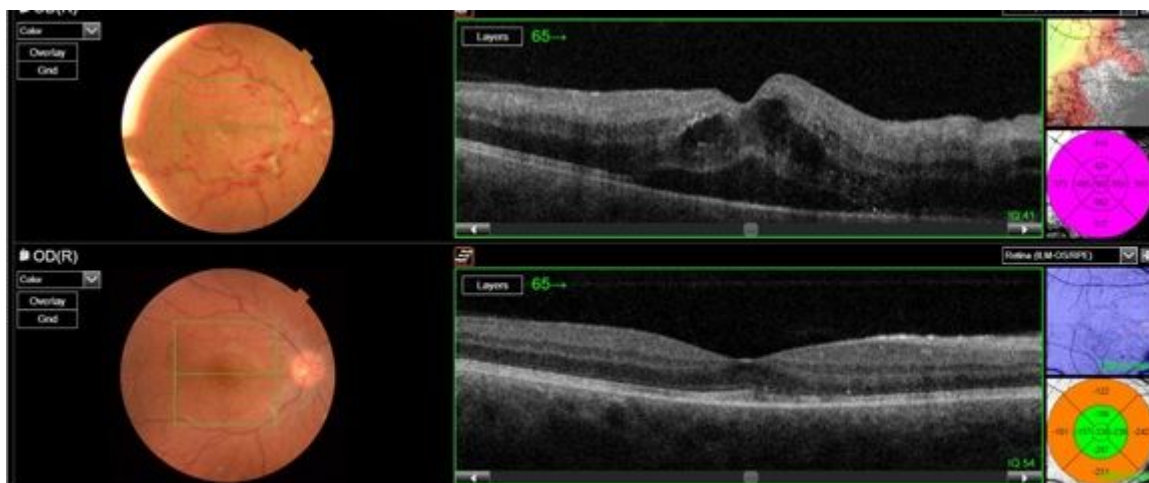


Figure 1

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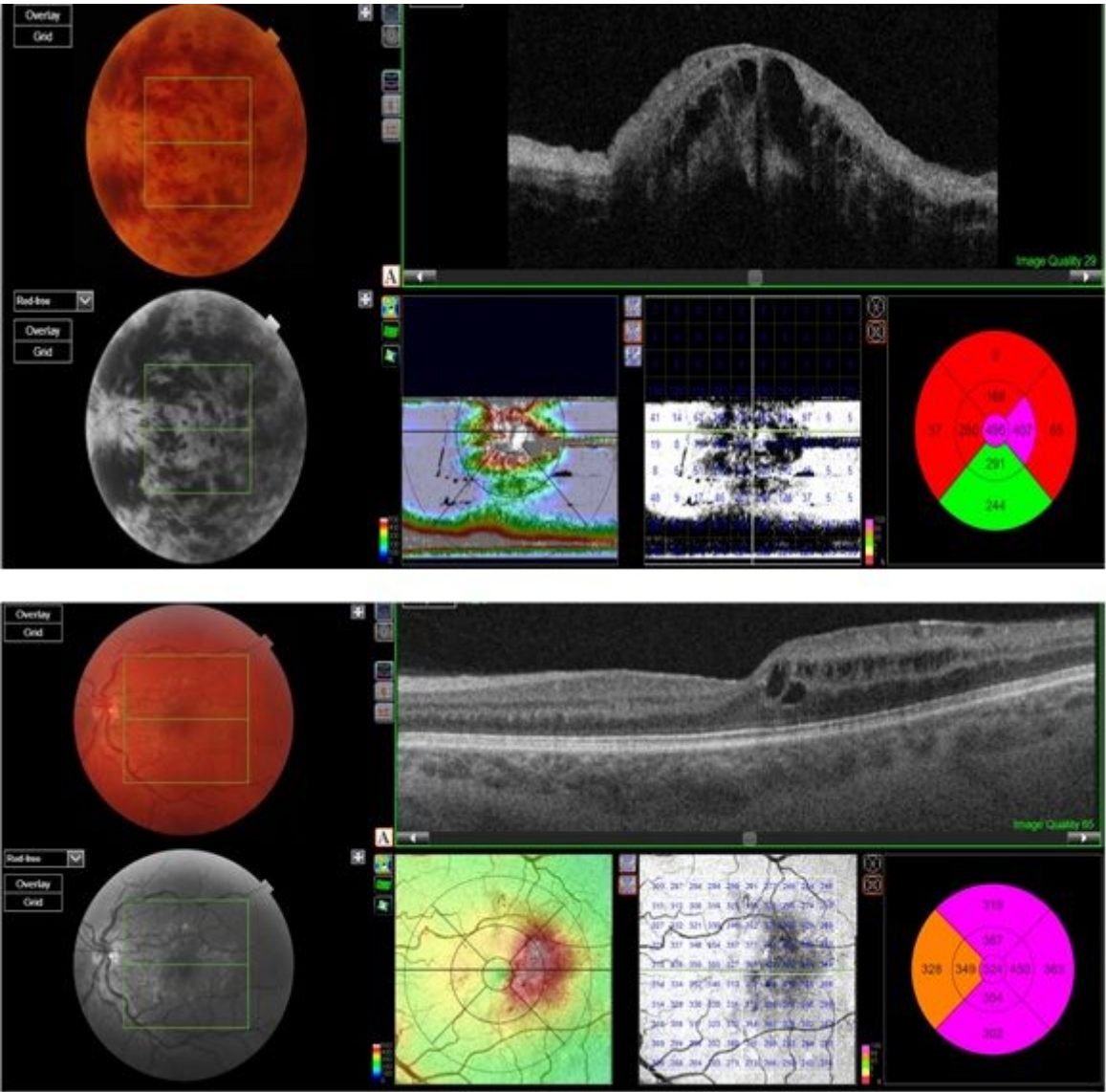


Figure 2

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