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Ranibizumab Monotherapy versus Ranibizumab Combined with Adjuvant Subthreshold Micropulse Yellow Laser in Treatment of Diabetic Macular Edema

Zeinab Sayed Hasan[1], Hamed Nasr El Den Taha[1], Mona El Sayed Aly[1], Tamer Mohammed Rady Emira[2]

[1]Ophthalmology Department, Al Zahraa University Hospital, Cairo, Egypt

[2]Ophthalmology Department, Military Eye Hospital, Cairo, Egypt

***Corresponding author:** Tamer Mohammed Rady Emira, **Mobile:** (+20) 01001456360, **E-mail:** tamiremira2004@hotmail.com

ABSTRACT

Background: Ranibizumab (RBZ) is a recombinant humanized antibody fragment that is active against all isoforms of VEGF-A, the most important players in the pathogenesis of diabetic macular edema (DME). Subthreshold 577 nm micropulse yellow laser (SMYL) was designed to fire a series of millisecond laser pulses in spaced-out intervals, reducing thermal retinal damage and allowing selective treatment to the RPE, preserving retina and reduced inflammation. Low-energy micropulse laser treatment allows tissue to cool between pulses to limit and confine the therapeutic photothermal effect within the tissue directly targeted by the laser.

Objective: A prospective comparative study between ranibizumab monotherapy versus ranibizumab combined with adjuvant SMYL in treatment of DME.

Patient and methods: A prospective randomized clinical study was done in military eye hospital. 120 eyes were presented by DME included in this study. 60 eyes treated by intravitreal RBZ (IVRBZ) monotherapy (RBZ group) and the other 60 eyes treated by IVRBZ with SMYL application (RBZ+SMYL group). Follow up of best corrected visual acuity (BCVA) and central macular thickness (CMT) for one year was done.

Results: It was found that BCVA was 0.25 ± 0.10 among RZB group and 0.27 ± 0.11 among RZB+SMYL group after 12 months. CMT was 307.78 ± 34.45 µm among RZB group and 287.07 ± 31.5 µm among RZB+SMYL group after 12 months.

Conclusion: Combined IVRBZ and SMYL are more effective in control of DME more than IVRBZ monotherapy.

Keywords: Ranibizumab, SMYL, DME.

INTRODUCTION

In the majority of industrialized countries, diabetic retinopathy (DR), is the primary cause of vision loss. Three processes account for diabetic macular ischemia (DMI), retinal neovascularization consequences (mostly vitreous hemorrhage and retinal detachment), and visual impairment [(1)].

A decline in central visual acuity is the most typical clinical sign of DME. However, it is now recognized that macular edema may persist without decreasing visual acuity yet observable on advanced retinal imaging (e.g. fluorescein angiography [FFA] and optical coherence tomography [OCT]). Additional clinical signs and symptoms include metamorphopsia and micropsia. While, macular edema may be treated with medication and surgery, persistent macular edema can lead to permanent damage to the photoreceptors, which would leave a permanent central scotoma [(2)].

DME can be caused by a variety of different mechanisms, including disruptions to the inner blood-retinal barrier (such as endothelial cell tight junctions), disruptions to the outer retinal barrier (such as RPE cell tight junctions), and/or disruptions to the normal outflow of retinal fluid by cells within the neurosensory retina [such as Muller cell dysfunction or retinal pigment epithelium (RPE) dysfunction] [(3)].

DME has a complicated, multifaceted etiology. Before any microangiopathy is clinically evident, intraretinal local inflammation produces neuronal injury. In particular, local releases of nitric oxide, TNF-α, interleukins, and vascular endothelial growth factor (VEGF) are facilitated by activated microglia. RPE transcytosis actively removes microglial cells, preventing a buildup of activated cells in the subretinal space. This active clearance reduces with DR, but rises with age to offset increased microglial activation to age-related debris [(4)].

One of the key actors in the pathophysiology of DME is VEGF. Bevacizumab, ranibizumab, and aflibercept are the three primary anti-VEGF medications used to treat DME. A humanized antibody fragment called ranibizumab is recombinant and effective against all VEGF-A isoforms [(5)].

Subthreshold 577 nm micropulse yellow laser (SMYL) was designed to fire a series of millisecond laser pulses in spaced-out intervals, reducing thermal retinal damage and allowing selective treatment to the RPE, preserving retina and reduced inflammation. With SMYL laser the “duty cycle” is decreased, avoiding any thermal damage to the neurosensory retina, which may improve visual function after the procedure. Micropulse mode incorporates Iridex's patented technology that finely controls thermal elevation by "chopping" a continuous (CW) beam into an envelope of repetitive short pulses. Low-energy micropulse laser treatment allows tissue to cool between pulses to limit and confine the therapeutic photothermal effect within the tissue directly targeted by the laser. No tissue reaction is visible during or post-treatment [(6)].

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PATIENT AND METHODS

Prospective, randomized, comparative, interventional and hospital based study that was carried out in Ophthalmology Department of Al Zahraa University Hospital and Military Eye Hospital, Cairo, Egypt. Interviews and examinations were done in Military Eye Hospital Outpatient Department from April 2020 to September 2021. The study included 120 eyes of 100 patients with DME who were divided into two groups: The first one contained 60 eyes of 50 patients; 20 were males and 30 were females and the second group contained 60 eyes of 50 patients; 27 were males and 23 were females. The two groups received IVRBZ (LUCENTIS®) 0.3 mg (0.05 mL of 6 mg/mL solution) for intravitreal injection, Initial U.S. Approval: 2006) monthly until CMT ≤ 400 µm [7].

Then, the first group received monthly injections of IVRBZ monotherapy (RBZ group). The second group received one set of SMYL, after one month it was followed by monthly IVRBZ. The number of injections depended on anatomical and functional response. We stopped injection if CMT was 250-300 µm, we re-injected when CMT ≥ 300 µm and we did not re-applicate SMYL [Iridex IQ 577 micro pulse device, manufactured by Iridex – USA]. The mainster focus grid contact lens was used for laser. All examples had fixed treatment parameters: 200 µm spot size, 200-ms exposure length, 400-mW power, and 5% duty cycle. A 7 x 7 grid pattern was applied to the whole edematous region, including the fovea (figure 1). The two groups completed 12 months follow-up postoperatively.

Figure (1): SMYL treatment parameters.

Inclusion criteria: Eyes confirmed of having DME with CMT ≥ 300 µm. No previous retinal treatment either injection or laser. No history of cataract or cataract surgery over the previous three months. No history of vitrectomy or other intraocular surgeries.

Exclusion criteria: Patients under 40 years of age and over 65 years old. History of intracocular surgeries, eye trauma, retinal laser, glaucoma, or uveitis. Macular edema due to causes other than diabetes. History of retinal detachment or vitreous hemorrhage due to intravitreal injection. Patients discontinue participation in the study.

METHODS

All patients were subjected to the followings:

1) Full history taking. **2)** General and local examination. **3)** Laboratory investigations. **4)** Visual acuity (log-MAR). **5)** Slit lamp examination: by Zeiss ® SL 800 slit lamp (To exclude neovascularization). **6)** IOP measurement: by Goldmann applanation tonometer (Haag-Streit ® 900). **7)** Gonioscopy: by Volk ®four mirrors goniolens. **8)** Fundus examination: by 90 degrees Volk® fundus lens. **9)** Heidelberg ocular coherence tomography (OCT), by SD-OCT Heidelberg engineering (Heidelberg, Germany) (Figure 2).

Figure (2): Heidelberg ocular coherence tomography, Kobry El Qubba military eye hospital, Cairo**.**

Treatment technique:

1. For Intravitreal ranibezumzb:

- Procedure was done in operating theater under complete sterile conditions.
- Benoxinate HCL 0.4% eye drops provide topical anesthetic.
- Insertion of a lid speculum.
- Sterilization of the eyes with 5% betadine eye drops and bandaging.
- In patients who were phakic, RBZ was injected into the pars plana using a 28-gauge needle 4 mm behind the limbus, and in patients who were pseudophakic, 3.5 mm.
- The patient is instructed to gaze away from the injection location by 180 degrees.

- Aiming for the mid-vitreous cavity, the needle was entered smoothly and once at the designated location.
- Securing the syringe withdrawal with a cotton swab tip to stop vitreous or Lucentis from refluxing from the injection site.
- Shortly after the injection, central retinal artery perfusion and IOP were measured; if the latter was noticeably elevated, paracentesis was performed.
- The eye speculum is removed.
- Applying eye ointment (a steroid and antibiotic mixture).
- Using sterile dressings to patch up eyes.
- For five days, a topical antibiotic (5 mg/ml) was provided four times a day.
- At 1, 3, and 7 days following injection, the patients' anterior and posterior segments were evaluated, their BCVA was measured, and their IOP was assessed in order to keep an eye out for any possible injection-related problems.

2. For SMYL application:

- Procedure was performed by Iridex IQ 577 micro-pulse device.
- The laser's settings were set at 400 mW of power, 200 ms of exposure time, 200 µm spot size, and 5% duty cycle.
- Confluent applications with no spacing were administered using 7 × 7 grid pattern over the entire macula and applied confluently to cover the whole area of macular edema using an Ocular Mainster (standard) focal lens (Ocular Instruments Inc, Bellevue, WA, USA).
- Every eye received 1000-1200 laser shots /set.

Follow up: BCVA and CMT for each patient were examined preoperatively and followed up three months, six months and 12 months postoperatively.

Ethical approval: Al Zahraa University Hospital and Military Eye Hospital Ethics Committees accepted this study (Study ID No. 1860). After receiving all of the information, each participant signed a permission. The Helsinki Declaration was followed up throughout the study conduct.

Statistical analysis

SPSS version 23.0 was utilized for the analysis of the recorded data. The ranges and mean ± SD of the quantitative data were displayed. Quantitative variables were also shown as percentages and numbers. Using the Shapiro-Wilk and Kolmogorov-Smirnov tests, data were examined for normality. When comparing two means, the independent-samples t-test of significance was employed. An analysis of significance using paired samples t-test was performed when comparing related samples. When comparing groups using qualitative data, the X^2-test and Fisher's exact test were used rather than the X^2-test alone in cases where the predicted count in any given cell was less than 5. The allowable margin of error was set at 5%, while the confidence interval was set at 95%. A significant p-value is considered when the value is at or below 0.05.

RESULTS

This prospective randomized corporative interventional hospital based study involved 120 eyes of 100 patients with DME. They were divided into two groups: The first one contained 60 eyes of 50 patients; 20 were males and 30 were females, while the second group contained 60 eyes of 50 patients; 27 were males and 23 were females and mean age in RZB group was 51.00 ± 4.50 comparing to RZB+SMYL groups that was 50.86 ± 4.52 years (Figure 3).

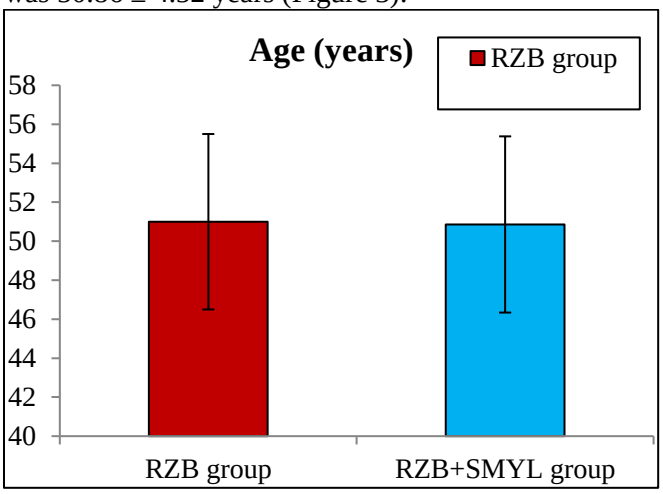

Figure (3): Comparison between RZB group and RZB+SMYL group according to Age (years).

It was found that the mean value of BCVA preoperatively was 0.17 ± 0.05, mean after 3 months was 0.21 ± 0.07, mean after 6 months was 0.23 ± 0.09 and mean of after 12 months was 0.25 ± 0.10 among RZB group. Also, the mean value of BCVA preoperatively was 0.17 ± 0.05, mean after 3 months was 0.21 ± 0.07, mean of after 6 months was 0.25 ± 0.09 and mean of after 12 months was 0.27 ± 0.11 among RZB+SMYL group. There was no statistically significant difference between groups according to BCVA (p-value >0.05) (Figure 4).

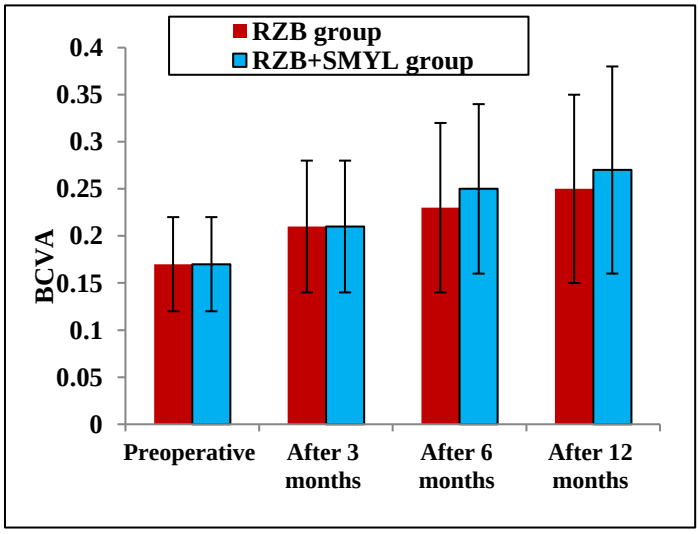

Figure (4): Comparison between RZB group and RZB+SMYL group according to BCVA.

It was found that the mean value of CMT in RZB group preoperatively was 363.53 ± 23.83, mean after 3 months

was 330.23 ± 21.72, mean of after 6 months was 311.70 ± 31.93 and mean after 12 months was 307.78 ± 34.45. Also, the mean value of CMT in RZB+SMYL group preoperatively was 358.10 ± 22.03, mean after 3 months was 315.40 ± 20.45, mean after 6 months was 291.52 ± 27.86 and mean after 12 months was 287.07 ± 31.51. There was a statistically significant lower mean value of CMT in RZB+SMYL group compared to RZB group after 3 months, after 6 months and after 12 months (p-value <0.001) (Figure 5).

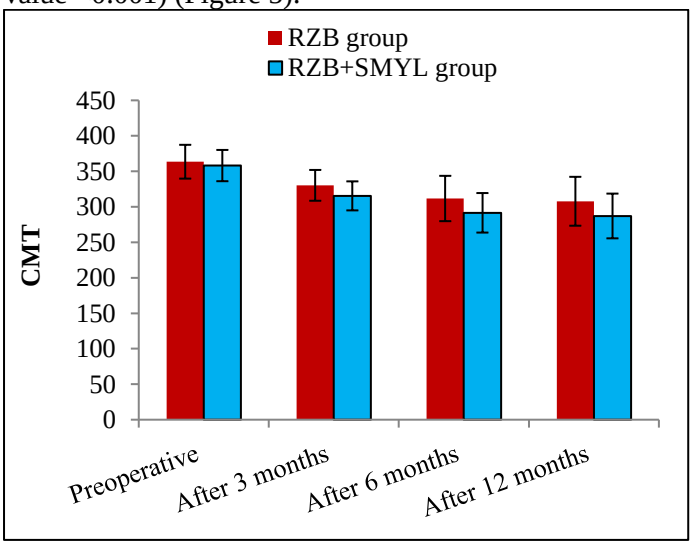

Figure (5): Comparison between RZB group and RZB+SMYL group according to CMT**.**

DISCUSSION

A total of 120 eyes of 100 patients were included in the study. They had attended the final follow up one year post-operatively. There were no significant differences between the two groups in terms of age, gender, eye laterality, diagnosis, preoperative visual acuity and OCT parameters.

According to the ETDRS, patients with CSME who had laser treatment had better visual acuity, a lower risk of vision loss, and very little visual field loss [(4)]. Conventional photocoagulation causes persistent chorioretinal scarring, macular haemorrhage, choroidal neovascularization, loss in visual acuity and contrast sensitivity, and visual field abnormalities [(8)]. **Mainster** [(9)] attempted to reduce chorioretinal damage by adjusting laser settings and clinical outcomes. He suggested that laser effects may be localized by reducing the laser wavelength, spot size, and exposure period, as well as using threshold or subthreshold therapy techniques. Problems with short-pulse treatment regimens can be avoided by utilizing repeatedly pulsed laser photocoagulation.

The present study showed improvement in the mean value of BCVA at three, six and 12 months in the two groups without reaching statistical significance. RZB+SMYL group showed more improvement in the mean BCVA than in RZB group at three, six and 12 months, without reaching clinical statistically significant difference. It is like the prospective randomized study of **Yin *et al.*** [(10)], which included total of 130 eyes with DME (CMT ≤ 400 µm). Patients with DME were randomly assigned to the IVRBZ monotherapy group (n = 65) or the IVRBZ + SMYL combination therapy group (n = 65). The main outcome measures were evaluated along 12 months. It showed improvement in the mean value of BCVA after three, six and 12 months in the two groups without reaching statistical significance. RZB+SMYL group showed more improvement in the mean BCVA than in RZB group at three and six months, while there was no difference at 12 months between the 2 groups, without reaching clinical statistically significant difference.

In a study of **Zhou *et al.*** [(11)]**,** which included a total of 90 eyes with DME (CMT ≤ 300 µm). Patients with DME were randomly assigned into the IVRBZ monotherapy group (n = 45) or the IVRBZ + SMYL combination therapy group (n = 45). The main outcome measures were evaluated along six months. It showed improvement in the mean value of BCVA after one, three and six months in the two groups without reaching statistical significance. RZB+SMYL group showed more improvement in the mean BCVA than in RZB group at 3 months, while there was no difference at six months between the two groups, without reaching clinical statistically significant difference. Their findings are consistent with the findings of the present investigation.

In a prospective randomized study of **Chen *et al.*** [(12)], which included total of 100 eyes with DME (CMT ≤ 400 µm). Patients with DME were randomly assigned into the IVRBZ monotherapy group (n = 50) or the IVRBZ + SMYL combination therapy group (n = 50). The main outcome measures were evaluated along three months. It showed improvement in the mean value of BCVA after one and three months in the two groups without reaching statistically significant difference. RZB group showed more improvement in the mean BCVA than RZB+SMYL group at one month, while there was no difference at three months between the two groups, without reaching clinical statistically significant difference. Their findings conflict with those of the current study.

The present study showed a reduction in the mean value of CMT after three, six and 12 months in the two group without reaching statistically significant difference. RZB+SMYL group showed more reduction in the mean CMT than in RZB group at three, six and 12 months, without reaching clinical statistically significant difference. It is similar to the prospective randomized study of **Cornish *et al.*** [(13)], which included total of 80 eyes with DME (CMT ≤ 300 µm). Patients with DME were randomly assigned to the IVRBZ monotherapy group (n = 40) or the IVRBZ + SMYL combination therapy group (n = 40). The main outcome measures were evaluated along 6 months. It showed reduction in the mean value of CMT after three and six months in the two groups without reaching statistically significant difference. RZB+SMYL group showed more reduction in the mean CMT than RZB group at

three and six months, without reaching clinical statistically significant difference.

In a prospective randomized study of **Mitani *et al.*** [14] that included a total of 120 eyes with DME (CMT ≤ 400 µm). Patients with DME were randomly assigned into the IVRBZ monotherapy group (n = 60) or the IVRBZ + SMYL combination therapy group (n = 60). The main outcome measures were evaluated along 9 months. It showed reduction in the mean value of CMT after one, three, six and 9 months in the two groups without reaching statistically significant difference. RZB+SMYL group showed more reduction in the mean CMT than in RZB group at one and three months, while there was no difference at six and 9 months between the two groups, without reaching clinical statistically significant difference. Their findings are consistent with the findings of the current investigation.

In a prospective randomized study of **Bıçak *et al.*** [15], which included total of 60 eyes with DME (CMT ≤ 400 µm). Patients with DME were randomly assigned into the IVRBZ monotherapy group (n = 30) and the IVRBZ + SMYL combination therapy group (n = 30). The main outcome measures were evaluated along 12 months. It showed reduction in the mean value of CMT after three, six and 12 months in the two groups without reaching statistical significance. There was no difference at three, six and 12 months between the two groups, without reaching clinical statistically significant difference. Their findings conflict with those of the current study.

There was a negative correlation between preoperative CMT and various periods of follow up. The line is straight denoting regular reduction in the mean CMT.

As there was no retinal or foveal damage whether clinically or by OCT when SMYL is used even in the fovea, SMYL may substitute the conventional laser treatment for DME.

CONCLUSION

In conclusion, combined IVRBZ and SMYL wee more effective in control of DME more than IVRBZ monotherapy. The difference was more obvious in the period of six months following treatment, but it was not so after one year of follow up.

Conflict of Interests: No conflict of interests.
Fund: None.

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