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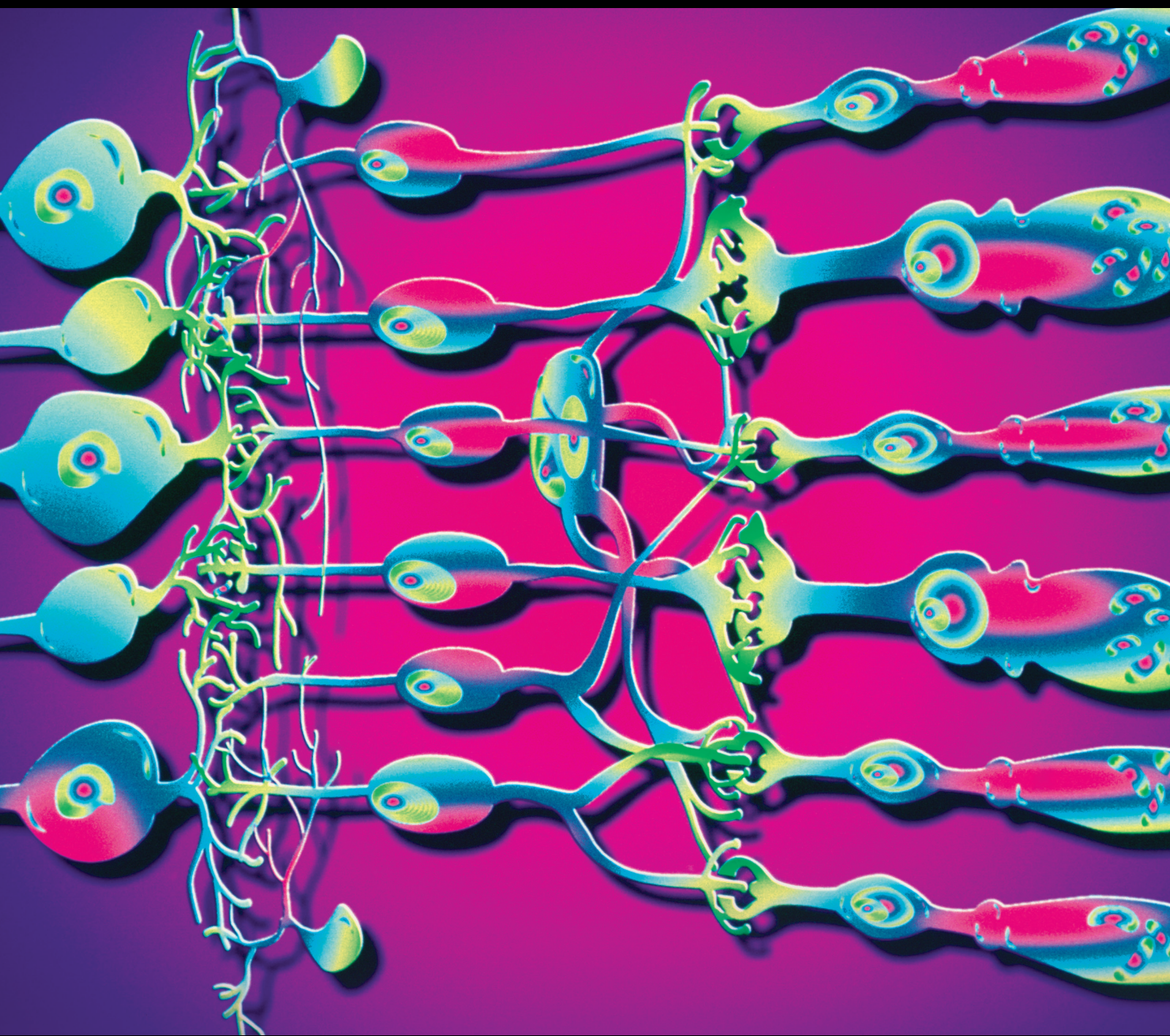
Retinal Laser Therapy in the Era of Anti-VEGF

Guest Editors: Raffael Liegl, Marcus Kernt, Jay Chhablani, and Kathrin Hartmann



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Editorial Board

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Research Article

Patient Preferences with Regard to Laser versus Intravitreal Injections in the Treatment of Diabetic Macular Edema

Lauren Mason, Jason N. Crosson, John O. Mason III, and Gerald McGwin Jr.

Retina Consultants of Alabama, University of Alabama at Birmingham School of Medicine, Callahan Eye Hospital, 700 18th St. South, Suite 707, Birmingham, AL 35233, USA

Correspondence should be addressed to Jason N. Crosson; jncrosson@gmail.com and John O. Mason III; masonallmason@yahoo.com

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Purpose. To identify treatment preferences of patients with diabetic macular edema (DME) having undergone laser and intravitreal injections. *Methods*. Patients with DME who received lasers and injections were surveyed, measuring preferences toward specific treatments. 66/210 diabetic patients met the criteria for our survey assessing preference for lasers and/or injections, incorporating demographics and treatment preference questions. Outcome measures included treatment preference (laser or injections), how often patients are willing to be treated, and how much vision they will sacrifice to avoid being treated every month. *Results*. 66 patients completed the survey. The mean diabetes duration was 20.7 years, the mean retina follow-up was 4.4 years, and patients received a mean of 4.82 lasers and 4.86 injections. 56% preferred injections, 33% preferred laser, and 11% had no preference. Regarding treatment effectiveness, 38% found no difference, 36% chose laser, and 25% chose injections. Regarding anxiety, 56% reported injection anxiety. While 50% versus 38% reported that laser was easier than injections. 91% would give up zero lines on the eye chart, and 76% would come in 12 times yearly for treatment to maintain vision. *Conclusion*. Patients with DME have no profound preference regarding laser versus intravitreal injections but prefer aggressive treatment and are unwilling to sacrifice vision for less visits.

1. Introduction

Diabetic mellitus is quickly becoming an epidemic in the United States, with an estimated 29.1 million Americans diagnosed to date [1]. Visual complications that result from diabetes, such as diabetic retinopathy and diabetic macular edema, remain the primary causes of vision loss in the U.S. Diabetic macular edema (DME) is a common progressive eye disease that affects an estimated 750,000 American diabetic patients [2]. Because of this, DME has an enormous impact on the quality of life in these patients, affecting their ability to perform everyday tasks such as driving and holding a job, with resulting depression and anxiety [3]. Due to the growing number of diabetic patients being diagnosed with DME, studies have been done to examine current treatment protocols for these patients to determine the most effective way to maintain visual stability and improvement over a long-term treatment plan. Although there are studies such as Miller et al. that have looked at treatment recommendations for DME based on physician preference [4], no study to date has evaluated actual patient preferences with regard to focal grid laser and intravitreal injections. The objective of our study was to perform a patient survey to identify the treatment preferences of patients with DME that had already been treated with both focal grid laser and bevacizumab intravitreal injections. Furthermore, we wished to identify how often patients are willing to be treated, which treatment they prefer (laser or injections), and how much vision they are willing to lose to avoid being treated every month.

2. Methods

After IRB approval, we conducted a single-center patient preference survey on patients with DME who had previously been treated with both focal grid lasers and bevacizumab intravitreal injections.

We consecutively evaluated 210 patients with diabetic retinopathy and found 66 who met entry criteria for our survey study. The entry criteria were patients over the age of 18 who could give informed consent to participate and who had prior focal grid laser treatment and intravitreal injections for DME. Exclusion criteria included prior panretinal photocoagulation (PRP) for proliferative diabetic retinopathy (PDR). Patients were given a 21-question survey (Table 1) that assessed patient preference for focal grid lasers and/or intravitreal injections. The survey included demographic features such as age, race, gender, socioeconomic status, transportation issues, employment and education, insurance provider, and disability status to analyze whether these factors correlated with the results regarding the primary outcome measures as listed on the survey.

Survey questions included the following: which treatment, focal grid laser or injection, made you more anxious before and after the procedure; which hurts more; which works better; which do you prefer; which is easier; how many lines on the eye chart would you be willing to lose to receive fewer treatments; would you be willing to come in every month for treatment; and which treatment allows you to drive from the office after being treated. Patients were also asked if they would choose monthly injections with better vision compared to 4 visits with focal grid laser and slightly less vision.

Primary outcome measures of this study included which treatment was preferred (lasers or injections), how often patients are willing to be treated, and how much vision they are willing to sacrifice to avoid being treated every month.

All lasers done in the past were performed in a standard modified Early Treatment Diabetic Retinopathy Study (ETDRS) fashion [5]. All intravitreal injections were performed in a standard fashion using American Academy of Ophthalmology (AAO) protocols with topical anesthetic and 5% povidone iodine, without lid speculum, or draping the patient.

Statistical analysis was performed using chi square testing to compare choices on survey questions with different demographic subgroups. Baseline patient characteristics were summarized using frequencies and percentages, and patient treatment preference was estimated for each demographic subgroup. Association of demographic features with treatment preference were assessed using chi square tests. p values of 0.05 or less (two sided) were considered statistically significant.

3. Results

A total of 66 patient statuses post treatment with focal grid laser and bevacizumab injections for diabetic macular edema completed the survey. The mean patient age was 63 (range 30–91), with 34 (52%) males and 32 (48%) females participating. 35 (54%) patients were Caucasian, and 31 (46%) were African American. Patients had been diabetic for a mean of 20.7 years (range 3–53 years) and had been seeing a retina specialist (JOM) for a mean of 4.4 years (range 1, visit 20 years). Of the 66 patients, 45% (30/66) were insured by Medicare or Medicaid, 18% (12/66) were insured by BlueCross, 30% were insured by others, and 6% were uninsured. Patients surveyed had received a mean of 4.82 lasers (range 1–19) and 4.86 injections (range 1–25).

Results showed that 56% (37/66) of patients preferred injections, 33% (22/66) preferred focal grid laser, and 11% (7/66) had no preference. Regarding effectiveness of treatment of either focal grid laser or injections, 38% (25/66) of patients found no difference regarding effectiveness of treatment of either focal grid laser or injections, 36% (24/66) of patients reported that focal grid laser works better, and 25% (17/66) reported that injections work better. Regarding pretreatment anxiety, 56% (37/66) reported that injections caused more pretreatment anxiety. 50% (33/66) of patients also reported that focal grid laser treatment was easier for them to undergo, second to 38% (25/66) who reported injections were easier for them to undergo, and 12% (8/66) who had no preference.

Regarding vision, 83% (55/66) of patients said that they would be willing to have 15-16 injections to gain 2 lines of vision. When asked to pick monthly injections with slightly better vision or 4 visits with laser and slightly less vision, 78% (52/66) chose monthly injections with better vision, as opposed to 21% (14/66) who chose fewer visits with less visual gain. 86% (56/66) of patients reported that they would be willing to sacrifice zero lines on the Snellen eye chart to receive 4 lasers as opposed to 15-16 shots, followed by 8% (5/66) who answered that they would sacrifice 2 lines and 6% (4/66) who would sacrifice one line on the Snellen eye chart. Regarding sacrificing lines on the Snellen eye chart in order to receive fewer treatments, 91% (60/66) said that they would sacrifice zero lines on the eye chart, and 76% (50/66) of patients would be willing to come in 12 times a year to receive treatment in order to maintain their vision.

Regarding employment status, 17/66 (26%) were employed, while 49/66 (74%) were unemployed. Mean BCVA was 20/70 for the employed group and 20/80 for the unemployed group, showing no statistical significance. The BCVA did not correlate with employment status.

Regarding those patients who were willing to sacrifice BCVA to receive fewer treatments, the mean BCVA was 20/60 and they had received a mean of 6.7 laser treatments and 3.5 injections. This was not statistically different from patients unwilling to sacrifice BCVA to receive fewer treatments (mean BCVA 20/70, mean lasers 4.82, mean injections 4.86).

Gender was a statistically significant factor as it pertains to pain tolerance and pain perception for focal grid laser and injections. Out of 18 patients who reported that focal grid laser hurt more than injections, 67% (12/18) of those were male patients. Furthermore, of the 27 patients who reported that either focal grid laser or injection was painful, only 37% (10/27) of those were male and 63% (17/27) were female. Males overwhelmingly chose fewer treatments and poorer vision as opposed to more treatments and better vision in a ratio 11 to 3 compared to female patients. Of those patients preferring fewer treatments, even if that meant having to sacrifice vision, 76% were male ($p = 0.0225$).

The questionnaire surveyed demographic factors, and 17% (10/59) of patients reported having transportation

Table 1: Patient DME survey.

Patient Name:
Age:
Race:
Gender:
Job/No Job:
Did they attend college:
How long they've been diabetic:
How long they have seen Dr. Mason:
Vision:
How many doctors do they have:
How many lasers have they received:
How many shots have they received:
Insurance carrier:
1. Which made you more anxious before you had either procedure (circle one): laser or shot
2. Which makes you more anxious now that you've had both (circle one): laser or shot
3. Which works better? (circle one) laser or shot
4. Which do you prefer? Laser or shot Why?
5. Which is easier for you? (circle one) laser or shot
6. If three lasers did not make you see quite as well as 15-16 shots, which would you pick? (circle one) Lasers or shots
7. How many lines on the eye chart would you be willing to give up in order to receive just 3 lasers as opposed to 15-16 shots?
8. Would you be willing to lose one line of vision on the eye chart so you didn't have to come in every month for a shot? Y N
9. Would you be willing to lose two lines of vision on the eye chart so you didn't have to come in every month for a shot? Y N
10. Would you be willing to lose three lines of vision on the eye chart so you didn't have to come in every month for a shot? Y N
11. Is it worth 15-16 shots to gain on average 2 lines of vision? Y N
12. On a scale of 1-5, what is the chance you can visit for 15-16 shots over 2 years? (1=most likely; 5=least likely)
13. On a scale of 1-5, what is the chance you can visit for 7 shots and 3 lasers over 2 years? (1=most likely; 5=least likely)
14. On a scale of 1-5, what is the chance you can visit for 4 lasers over 2 years? (1=most likely; 5=least likely)

problems. 75% (49/66) of patients reported being unemployed, 45% (30/36) did not attend college, and 40% (27/66) also reported being on disability. There was a statistical significance between being unemployed and post-treatment anxiety for both lasers and injections. Those unemployed had more anxiety with receiving injections ($p = 0.036$). There was also statistical significance between employment and treatment preference between focal grid laser and injection. Those unemployed preferred to have laser treatment over injections compared to those with a job ($p = 0.0139$). Regarding pain after either laser or injections, males were more likely to have pain than females ($p = 0.05$).

4. Discussion

Diabetic macular edema is one of the leading causes of vision loss in diabetics in the United States. DME has a vast impact on the quality of life in patients suffering with this disease due to visual acuity loss over time. This vision loss can lead to inability to drive or hold a job, leading to psychological symptoms of depression and anxiety. Rees et al. examined the association between vision loss and DME with psychological outcomes such as symptoms of anxiety and depression in patients with diabetes. In their study, greater depressive symptoms correlated with more severe diabetic retinopathy, lower education level, poorer glucose control, and longer duration of diabetes, and greater symptoms of anxiety were reported with lower education level [3]. Our findings regarding employment and treatment anxiety correlated with these results. 75% (49/66) of patients surveyed reported being unemployed. This extremely high rate is possibly due to poor health secondary to their disease, the number of doctor visits per month, and the location of the study being rural Alabama. There was a statistical significance between being unemployed and posttreatment anxiety, showing that those who are unemployed show more anxiety with injections ($p = 0.036$). There was also statistical significance between employment and treatment preference between focal grid laser and injection. Those unemployed preferred to have laser treatment over injections compared to those with a job ($p = 0.0139$). This strong correlation between unemployment, anxiety, and treatment choice may lead retina physicians to consider these associations prior to treatment when considering lasers or injections for DME.

Our questionnaire surveyed demographic factors, and 17% of patients (10/59) reported having transportation problems. This could be due to socioeconomic status or a result of losing vision and the inability to drive. 75% (49/66) of patients reported being unemployed, 45% (30/36) did not attend college, and 40% (27/66) also reported being on

disability. Lower socioeconomic status may be substantial in contributing to transportation problems, lack of education of their disease, lack of a college education, disability, and low overall health management, leading to poorer vision and higher depressive symptoms long term. Our findings corroborate Rees et al. [3]. These results lead us to believe that socioeconomic status, transportation issues, education, employment, and disability are all significant factors seen in our survey that can be linked to severity of DME requiring many years of treatment.

We found that the majority of patients surveyed were unemployed, which may be due to a number of factors including the number of doctor visits they must make per month, diabetes affecting their ability to be employed, and their relatively poor visual acuity requiring frequent treatments by the ophthalmologist. We found no correlation between employment status and patient's BCVA. Therefore, our patient's visual acuity alone is not the determining factor for their employment status.

Those patients willing to sacrifice vision to receive fewer treatments had no difference in BCVA compared to those patients unwilling to sacrifice vision for fewer treatments. We found that there was no difference between number of treatments received by both groups. This implies that visual acuity and number of treatments received have no bearing on those patients who are willing to sacrifice vision to receive fewer treatments. Gender played a role as we will discuss in the following paragraph.

Gender differences were also statistically significant with regard to patient treatment preference. When asked if patients preferred an injection once a month for better vision or 4 laser treatments per year and slightly worse vision, 14/66 (21%) chose 4 lasers and slightly worse vision. Males overwhelmingly chose fewer treatments and poorer vision as opposed to more treatments and better vision. Of those patients preferring fewer treatments, even if that meant having to sacrifice vision, 76% were male ($p = 0.0225$). Regarding pain after either laser or injections, males were also more likely to have pain than females ($p = 0.05$). These findings lead us to believe that females have a higher pain tolerance when it comes to focal grid laser and injection for DME when compared to males. This supports the pain perception study performed by Frot et al. [6]. This study found that pain intensity, unpleasantness, and anxiety, especially as it pertains to the face, are much higher in men than in women [6]. Although men have lower overall pain ratings, they reported more pain-related anxiety and showed a more positive correlation between anxiety and pain intensity and unpleasantness than women. These results also explain why 56% (10/18) of men reported having posttreatment anxiety regarding injections as compared to 44% in women.

Regarding vision, 91% (60/66) said that they would sacrifice zero lines on the eye chart and 76% (50/66) of patients would be willing to come in 12 times a year to receive treatment in order to maintain their vision. Previous studies have identified a link between visual impairment, anxiety, and depressive symptoms [3, 7–9]. Our study lends further credence that sight is indeed precious and patients recognize this fact. Our patients, in general, are unwilling to sacrifice any vision regardless of the number of treatments or the type of treatments they must receive.

In conclusion, this is the first study to evaluate patient preferences for treatment with focal grid laser and intravitreal injection in diabetics with DME. The results of the survey show that there is no statistically significant difference between patient preferences for laser or intravitreal injection treatment, 76% of patients are willing to be treated a maximum amount of times in order to maintain their vision, and 91% would not give up any vision to receive fewer treatments. Patients express a strong overall preference for treatment schemes that allow the highest degree of visual acuity and stability that can be achieved. Treatment schemes that result in optimal visual outcomes are preferred, even if it involves a high treatment burden. A significant correlation was found between unemployment and gender with regard to treatment preference, suggesting that demographics also play a role in patient preferences toward DME treatment.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Combination of Anti-VEGF and Laser Photocoagulation for Diabetic Macular Edema: A Review

Laura N. Distefano, Jose Garcia-Arumi, Vicente Martinez-Castillo, and Anna Boixadera

Vall d'Hebron Hospital, Pg de la Vall d'Hebron 119, 08032 Barcelona, Spain

Correspondence should be addressed to Laura N. Distefano; lndistefano@vhebron.net

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Diabetic macular edema (DME) is the most common cause of vision loss in diabetic patients. Thirty years ago, the Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that focal/grid laser photocoagulation reduces moderate vision loss from DME by 50% or more; thus, macular photocoagulation became the gold standard treatment for DME. However, with the development of anti-VEGF drugs (bevacizumab, ranibizumab, and aflibercept), better outcomes were obtained in terms of visual acuity gain and decrease in macular thickness in some studies when antiangiogenic drugs were administered in monotherapy. Macular laser therapy may still play an important role as an adjuvant treatment because it is able to improve macular thickness outcomes and reduce the number of injections needed. Here, we review some of the clinical trials that have assessed the efficacy of macular laser treatment, either as part of the treatment protocol or as rescue therapy.

1. Introduction

More than four hundred million adults suffer from diabetes mellitus worldwide [1]. Ninety percent of diabetic patients will have some form of retinopathy twenty-five years following diagnosis [2]. Diabetic retinopathy causes blood-retinal barrier breakdown, leading to increased permeability and leakage from retinal capillaries. Fluid accumulates within the retinal layers, resulting in a thickened macula. Diabetic macular edema (DME) is the most common cause of vision loss in diabetic patients, with a prevalence that ranges from 19% to 65% [3]. This paper reviews the current role of laser for DME in the era of antiangiogenic therapy.

2. Diabetic Macular Edema

Involvement or threatening of the center of the macula was termed clinically significant macular edema (CSME) by the Early Treatment Diabetic Retinopathy Study (ETDRS) [4, 5]. Furthermore, in the ETDRS, edema was classified as focal or diffuse by the proportion of leakage that came from microaneurysms graded in fluorescein angiograms: more than 66% or less than 33%, respectively. Severity of macular ischemia was also graded according to the degree of capillary loss in the central and inner subfields [6]. Nowadays, however, DME is mainly classified by its central involvement in most of the main clinical trials that evaluate intravitreal therapy for DME.

3. Macular Laser Photocoagulation

3.1. Treatment Techniques. In the ETDRS, two macular laser treatment techniques were defined: focal and grid, both performed between 500 and 3000 microns from the fovea but not within 500 microns from the papillary border [7, 8]. *Focal* laser was applied for focal lesions that not only included microaneurysms but also included intraretinal microvascular abnormalities (IRMA) and small capillaries with focal leakage. *Grid* laser was performed in areas of macular thickening with diffuse leakage or capillary loss.

Although effective, laser burns close to fixation were described to enlarge over time, potentially affecting the fovea, with secondary central visual loss, central scotomas, and altered color vision [9]. To avoid these potential complications, a modification of the described ETDRS technique was developed, called the modified-ETDRS laser treatment

(MLT) technique. In this modified protocol, a smaller spot of 50 μm size and 50 to 100 milliseconds burn duration is performed. *Focal* laser aims to treat only leaking microaneurysms, causing a mild gray-white burn but not necessarily a darkening or whitening of the microaneurysm. *Grid* laser is applied to areas with diffuse leakage or nonperfusion, with barely visible, two-burn widths apart laser burns [10]. This is currently the preferred technique in daily practice, especially focal laser for treating small areas of thickening, threating but not affecting the fovea. MLT is, likewise, the protocol of choice in the studies we will describe below.

3.2. Mechanism of Action. *Focal* laser is thought to reduce the leakage from the microaneurysm by direct occlusion of the lumen [11]. On the other hand, although the exact mechanism of the effect of *grid* photocoagulation is not well understood, some plausible theories have been described [12]: (a) destruction of photoreceptors which have high oxygen demands, (b) increased oxygenation of the retina through the laser scar, (c) restoration of new RPE barrier by spreading in small lesions and by proliferation in larger lesions, (d) production of cytokines TGF beta and PEDF from the stimulated RPE, (e) decrease in area of abnormal leakage: reduction in the leaking capillary area, and (f) autoregulation with secondary decrease in retinal blood flow and consequent decreased edema [13].

4. Clinical Trials of Diabetic Macular Edema

Several prospective, randomized, controlled clinical trials have been conducted in the past years regarding the treatment of DME involving the center of the macula. We review here some of the ones that have compared macular laser treatment as part of the treatment protocol or as rescue therapy.

4.1. Early Treatment Diabetic Retinopathy Study (ETDRS). In this classic study, patients with DME, visual acuity (VA) of 20/200 or better, and no proliferative retinopathy were randomized into early or deferred focal/grid photocoagulation [6]. DME eyes with CSME treated with laser had lower rates of visual loss compared with controls: 12 versus 24%, at 3 years. In diffuse edema, grid was of limited benefit: VA improved in 15%, worsened in 24%, and remained stable in 61% [4, 5]. Thus, the ETDRS demonstrated that focal/grid laser photocoagulation reduces moderate vision loss from DME by 50% or more, and from these results, it became the gold standard against which all new treatments have been compared to since then [4, 6].

4.2. Clinical Trials with Macular Laser as a Treatment Arm

4.2.1. Intravitreal Triamcinolone Acetonide and Focal/Grid Photocoagulation for Diabetic Macular Edema (DRCR.net Protocol B Study). One of the first drugs that was tested against laser treatment was intravitreal triamcinolone. In 2008, the first results from Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol B were published: eight hundred forty study eyes with VA of 20/40 to 20/320 were randomized to focal/grid photocoagulation, 1 mg or 4 mg intravitreal triamcinolone. Retreatment was administered for persistent or new edema at 4-month intervals. The results at 12 months showed no significant differences in mean VA gain among the three treatment arms. At the 2-year follow-up visit, mean VA change from baseline was clinically modest but statistically greater in the laser group (+1 ETDRS letter) than in the other 2 groups (−2 and −3 ETDRS letters; $p = 0.02$ and $p = 0.002$, resp.). This difference was observed even for those eyes that were pseudophakic at baseline and for those that were pseudophakic or had minimal or no cataract at the 2-year follow-up visit [14]. After three years of follow-up, VA letter score did not show any change in the triamcinolone groups but improved in 5 letters in the laser group [15]. Macular thickness in optical coherence tomography (OCT) decreased in a similar way. In terms of cataract formation, most eyes treated with 4 mg triamcinolone required surgery.

These results highlight the long-term effect of laser treatment monotherapy, as the outcomes in visual acuity and retinal thickness improved after three years of treatment.

4.2.2. Bevacizumab or Laser Therapy (BOLT Study). Two years later, the BOLT study evaluated intravitreal antiangiogenic 1.25 micrograms bevacizumab versus focal/grid photocoagulation in patients with persistent center-involving CSME and visual acuity of 20/40 to 20/320. Eighty eyes were randomized into receiving either bevacizumab alone (at 6-week intervals) or focal/grid alone (at 4-month intervals) [16]. At the 12-month follow-up visit, subjects treated with bevacizumab improved a median of 8 ETDRS letters, compared with the laser-treated eyes, which lost VA (−0.5, $p = 0.0002$), despite a median of 3 laser treatments being performed. Twelve percent of subjects treated with bevacizumab versus 5.3% treated with laser gained more than 15 letters. Consistently with VA results, central macular thickness (CMT) decreased 129 μm in the bevacizumab group ($p < 0.001$) compared with 68 μm in the laser group ($p = 0.02$).

At the 2-year follow-up visit, the bevacizumab arm maintained a median of +9 letters improvement, whereas laser-treated eyes showed better results than at 1-year visit (+2.5, $p = 0.005$). In terms of percentage of patients who gained 15 letters or more compared to baseline, the bevacizumab arm showed superiority compared to laser (32% and 4%, resp., $p = 0.004$). Mean reduction in central macular thickness was 146 μm in the bevacizumab arm versus 118 μm in the MLT arm [17]. Even though the follow-up was short, laser outcomes are slightly better during the second year compared with the first year.

4.2.3. VEGF-Trap-Eye in Patients with Diabetic Macular Edema (DA VINCI Study). This phase II clinical trial enrolled 221 diabetic patients, assigned to receive either 0.5 mg aflibercept every 4 weeks, 2 mg aflibercept every 4 weeks, 3 monthly injections of 2 mg aflibercept and then every 8 weeks, 3 monthly injections of 2 mg aflibercept and then on a PRN protocol, or macular laser photocoagulation alone.

All aflibercept groups gained VA ranging from a mean of +9.7 to +13.1 letters, while patients in the laser group

only lost a mean of 1.3 letters at 1-year follow-up. Mean reductions in CMT in the 4 aflibercept groups ranged from −165 to −227 μm compared with only −58 μm in the laser group ($p = 0.0066$, aflibercept arms versus laser) [18].

4.2.4. Intravitreal Aflibercept for Diabetic Macular Edema (VIVID/VISTA Studies). More recently, 872 eyes were enrolled in two identical phase III trials that randomized them into receiving 2 mg aflibercept every 4 weeks, 5 monthly injections of 2 mg aflibercept and then every 8 weeks, or focal/grid laser. Mean VA improvement from baseline to week 100 was the lowest in the laser groups (+0.9 and +0.7) compared with that of both aflibercept arms (+11.5 and 11.4 for aflibercept every 8 weeks; +11.4 and +9.4 for aflibercept every 8 weeks) for VIVID and VISTA, respectively. The proportion of the eyes that gained 15 letters or more from baseline at week 100 was 38%, 33%, and 13% ($p < 0.0001$) in VISTA and 38%, 31%, and 12% ($p < 0.0001$) in VIVID [19].

DA VINCI and VIVID/VISTA show poor short-term results of laser alone in terms of visual acuity.

4.2.5. Ranibizumab for Edema of the Macula in Diabetes (READ-2 Study). The READ-2 study added the combination therapy as a treatment arm. For the first 6 months of the study, 126 patients with DME were randomized to receive 0.5 mg ranibizumab every two months, focal/grid laser photocoagulation at baseline and at month 3 if needed, or a combination of 0.5 mg of both at baseline and month 3. At month 6, the mean gain in BCVA was significantly greater for ranibizumab monotherapy (+7.24 letters, $p = 0.01$) compared with laser alone (−0.43 letters); combination therapy showed no differences when compared to the other two (+3.80 letters). Twenty-two percent, 0%, and 8% of the subjects improved 15 letters or more ($p = 0.002$). CMT was reduced as well by 50%, 33%, and 45% in groups 1, 2, and 3, respectively [20].

After month 6, all subjects were allowed to be treated with ranibizumab. Fewer injections were needed during the 18-month follow-up for the combination group (2.9) compared with ranibizumab alone (5.3) and laser alone (4.4) original groups. At 24 months, mean improvement in BCVA remained stable for ranibizumab-treated patients (+7.7) but was better for laser alone (+5.1) and combination therapy (+6.8). The percentage of patients who gained 15 letters or more of BCVA also improved for the laser and ranibizumab plus laser-treated eyes, compared to the 6-month results (24%, 18%, and 26% for ranibizumab, laser, and combination, resp.). In terms of mean CMT at the 24-month visit, combination therapy showed the better results: 258 microns, compared with 340 μm achieved with ranibizumab and 286 μm with laser alone [21].

At the 36-month visit, mean improvement from the baseline BCVA was greater compared to the 24-month results in the ranibizumab group (+10.3 letters). Laser (+1.4 letters) and combination (+8.9 letters) groups showed more stable results when compared with the 2-year results. However, CMT showed greater reduction with combination therapy (−243 μm) than with laser alone (−193 μm) or ranibizumab alone (−132 μm). The mean number of ranibizumab injections was greater in the ranibizumab arm compared with the laser arm (5.4 versus 2.3 injections, $p = 0.008$) but not compared with the ranibizumab plus laser arm (3.3, $p = 0.11$) [22].

In brief, 3-year outcomes of combination therapy showed the greatest CMT reduction, greater VA change than laser but no ranibizumab, and fewer injections needed than ranibizumab monotherapy.

4.2.6. Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema (RESTORE Study). Similar to the READ-2 study, combination therapy was included in this protocol: 345 diabetic patients with visual impairment due to DME were randomized to 0.5 mg ranibizumab (group 1), 0.5 mg ranibizumab plus laser (group 2), or sham injections plus laser (group 3). Ranibizumab was given monthly for the first 3 months then pro re nata (PRN); laser was given at baseline then PRN. Mean average change in BCVA letter score from baseline to month 1 through 12 was +6.1 and +5.9 versus +0.8 for groups 1, 2, and 3 (both $p < 0.0001$). No differences were found when comparing focal and diffuse types of edema. At month 12, 22.6%, 22.9%, and 8.2% gained more than 15 letters in the three groups, respectively. The mean central retinal thickness was significantly reduced from baseline with ranibizumab (−119 μm) and ranibizumab plus laser (−128 μm) versus laser (−61 μm; both $p < 0.001$) [23].

In the extension study [24], patients were eligible to receive ranibizumab and concomitant laser treatment. In the prior laser group, a progressive BCVA improvement (+6.0 letters) and CMT reduction (−142.7 μm) at month 36 were observed after allowing treatment with ranibizumab. The prior ranibizumab and ranibizumab plus laser groups improved +8 and +6.7 letters compared to baseline and showed 142 and 146 microns CMT reduction, respectively. Medians of 6 (mean of 6.8) and 4 (mean of 6) injections were performed in the prior ranibizumab and ranibizumab plus laser groups, respectively.

In the RESTORE study, combination therapy achieved similar anatomical outcomes compared to ranibizumab monotherapy but less VA improvement, with a small difference in injection number.

4.2.7. Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy in Asian Patients with Diabetic Macular Edema (REVEAL Study). In this study, 396 Asian diabetic patients were randomized to 0.5 mg ranibizumab, 0.5 mg ranibizumab plus laser, or sham injections plus laser. Greater BCVA improvements were achieved at 12 months in both ranibizumab 0.5 mg groups (+5.9 and +5.7 letters), compared with laser monotherapy (+1.4 letters). Mean CMT reduced significantly from baseline to month 12 with ranibizumab (−134.6 μm) and ranibizumab + laser (−171.8 μm) versus laser (−57.2 μm). A mean of 7.8 and 7 injections was received in the ranibizumab and ranibizumab + laser arms, respectively.

Although not statistically significant, combination therapy achieved better outcomes in terms of anatomical resolution of

edema, with slightly less injections needed but similar BCVA change compared to ranibizumab monotherapy.

4.2.8. Ranibizumab 0.5 mg Treat-and-Extend Regimen for Diabetic Macular Edema (RETAIN Study). Treat-and-extend (T&E) approach progressively increases visits and intravitreal injections intervals when BCVA stability is achieved. This single-masked multicentric study aimed to demonstrate the noninferiority (four-letter margin mean average change in BCVA) of this regimen compared to PRN from baseline to months 1 through 12. Patients were randomized to PRN, T&E, or T&E plus focal/grid laser. The latter group received laser treatment on day 1 followed by retreatment at investigator's discretion, with a 3-month minimum interval recommended between treatments. Both T&E regimens were noninferior to PRN based on mean average BCVA change from baseline to months 1 to 12 (T&E plus laser +5.9 and T&E +6.1 versus PRN +6.2 letters; both $p < 0.0001$). At month 24, no differences were found between either groups, but T&E plus laser and PRN showed slightly better results than T&E alone (mean BCVA +8.3 and +8.1 versus +6.5 letters, resp.). The mean number of injections was similar in both T&E approaches (12.4 and 12.8 in the T&E plus laser and T&E groups) but higher than the PRN group (10.7).

In this study, second-year results showed a tendency toward better visual outcomes with treat-and-extend regimen when associated with laser instead of ranibizumab T&E monotherapy.

4.2.9. Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema (DRCR.net Protocol I Study). In 2010, DRCR network published the first results of a trial comparing sham injections plus prompt laser, 0.5 mg ranibizumab plus prompt laser, 0.5 mg ranibizumab plus deferred laser (24 or more weeks), or 4 mg triamcinolone plus prompt laser in 854 study eyes with visual acuity of 20/32 to 20/320. At 1-year follow-up, sham injections plus prompt laser and triamcinolone plus prompt laser achieved the lowest results in terms of mean change in the VA letter score from baseline: +3 and +4, respectively; on the contrary, ranibizumab groups gained a mean of +9 letters in this period of time. In the subset of pseudophakic eyes at baseline, visual acuity improvement in the triamcinolone plus prompt laser group was similar to that in the ranibizumab groups [25]. The expanded 2-year results reported were similar to these results [26].

Sixty-seven percent of the eyes completed the 5-year follow-up. While the ranibizumab arms continued to be treated as the original protocol stablished, the laser alone and triamcinolone plus laser groups were able to be treated with ranibizumab as early as 74 weeks from baseline, for persistent DME with vision impairment. Mean change in ETDRS letter scores from baseline in the four groups was +5, +8, +10, and +7 (original laser, ranibizumab plus laser, ranibizumab plus deferred laser, and triamcinolone plus laser groups, resp.). Original laser group achieved the greatest CMT reduction at 5 years from baseline (−196 microns) compared with ranibizumab and triamcinolone groups (−152, −160, and −40 microns, resp.) [27].

Although ranibizumab plus deferred laser achieved the best VA outcomes, it is noteworthy that ranibizumab plus prompt laser-treated eyes reached similar 5-year VA with lower number of injections needed (median of 17 versus 13, resp.) and a median of 3 focal/grid photocoagulation treatments. Furthermore, the original laser group achieved the best results in terms of CMT reduction.

4.3. Clinical Trials with Macular Laser as a Rescue Treatment

4.3.1. Ranibizumab for Diabetic Macular Edema (RISE/RIDE Studies). Adults with vision loss from DME (BCVA 20/40–20/320 Snellen equivalent) and central subfield thickness of 275 or more were randomized to monthly sham, 0.3 mg or 0.5 mg ranibizumab injections. From month 3, all patients were evaluated monthly for the need for macular laser. Grid or focal photocoagulation directly to microaneurysms with proven leakage in areas of retinal edema was performed if CMT was 250 μm or more; there was less than 50 μm change from the previous visit and the investigator believed it would be of benefit. The mean number of macular laser treatments over 24 months was 1.8 for the sham group and 0.8 in both ranibizumab groups. In RISE, at 24 months, 18% of sham patients gained 15 or more letters versus 45% of 0.3 mg ($p < 0.0001$) and 39% of 0.5 mg ($p < 0.001$) ranibizumab patients. In RIDE, more patients treated with ranibizumab gained 15 letters or more: 12% of sham patients versus 34% of 0.3 mg patients ($p < 0.0001$) and 46% of 0.5 mg ranibizumab patients ($p < 0.0001$). Significant decreases in retinal thickness were achieved, and retinopathy was more stable in the ranibizumab-treated group [28].

In the third year, sham patients, while still masked, were eligible to be treated with monthly 0.5 mg ranibizumab. VA outcomes and reductions in CMT seen at month 24 in the ranibizumab groups remained stable through the last visit. On the other hand, after being treated with ranibizumab, average VA gains in the sham group were lower compared with the gains seen in the ranibizumab patients after 1 year of treatment (+2.8 versus +10.6 and +11.1 letters for prior sham, 0.3 mg and 0.5 mg ranibizumab, resp.) [29].

Once again, laser monotherapy probes to be less effective in improving VA: although 74 and 70% of patients received focal/grid laser during the first 24 months of follow-up in the sham groups, compared to 39 and 36% for 0.3 mg ranibizumab and 35 and 18% for 0.5 mg ranibizumab, final VA in this group was worse than in the ranibizumab groups. The influence of macular laser in number of injections is not evidentially because of the monthly based regimen of the protocol.

4.3.2. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema (DRCR.net Protocol T Study). Protocol T was the first study designed to compare PRN 2 mg aflibercept, 1.25 mg bevacizumab, and 0.3 mg ranibizumab in center-involved DME in 660 patients.

Although laser treatment was not part of study arms, it was performed after 6 months if DME persisted. Aflibercept group received fewer laser treatments (41%), compared with bevacizumab and ranibizumab groups during the 2 years of

follow-up (64% and 52%, resp.) (aflibercept versus bevacizumab, $p < 0.001$; aflibercept versus ranibizumab, $p = 0.04$; bevacizumab versus ranibizumab, $p = 0.01$). Fewer injections were needed during the second year of follow-up in all groups: 5, 6, and 6 compared with 10, 10, and 9 for aflibercept, bevacizumab, and ranibizumab, respectively. Aflibercept-, bevacizumab-, and ranibizumab-treated eyes showed VA improvement from baseline to 2 years, but VA outcomes among the eyes with worse baseline VA were better with aflibercept compared with bevacizumab but not compared with ranibizumab. Similarly, CMT decreased on average by 171, 126, and 149 microns for aflibercept, bevacizumab, and ranibizumab, respectively [30].

Even though aflibercept-treated eyes received less laser treatment, it is not possible to assess the separate effect of macular laser on visual and anatomical outcomes in each treatment arm because it was part of the treatment regimen in this study.

5. Conclusions

Since the ETDRS showed that focal/grid laser photocoagulation reduced moderate vision loss from DME by 50% or more, laser became the gold standard for the treatment of DME. Twenty-five years later, intravitreal triamcinolone showed no long-term benefit in VA improvement; thus, laser continued to be the first-line treatment option for DME. However, since the development of anti-VEGF drugs, better VA results were obtained as well as a greater decrease in macular thickness when antiangiogenic drugs alone were compared with laser monotherapy. Currently approved ranibizumab (0.3 mg in the USA and 0.5 mg in Europe) and 2 mg aflibercept, as well as off-label 1.25 mg bevacizumab, have become nowadays the first-line therapy for center-involving DME.

However, macular laser therapy may still have an important role as an adjuvant treatment, as studies with bevacizumab, ranibizumab, or aflibercept have shown that a synergic effect can be achieved when laser is combined with antiangiogenics. Laser effect, despite being slower than antiangiogenics, can have a longer lasting effect and seems to increase over time while injections have more stable long-term results. Furthermore, combination therapy may reduce the chance of secondary engorgement of the laser burns, as the prompt effect of the antiangiogenic drying the macula reduces the intensity of the laser required. The change of macular thickness at the final visit from baseline may be further reduced when laser is added to injections, as described in READ-2 study with 3 years of follow-up; this has been also described in a short-term case series at 12 months (152 versus 143 microns reductions with bevacizumab monotherapy and combination therapy, resp.) [31]. Also, in DRCR.net Protocol I, prior laser monotherapy group with ranibizumab added from week 74, achieved the greatest CMT reduction at 5 years. In the Protocol T, to achieve a totally dry macula, laser needed to be done after six months of intravitreal therapy in 41%, 52%, or 64% of the patients treated with aflibercept, ranibizumab, or bevacizumab, respectively. However, in a meta-analysis of 12–36 months of follow-up studies, no differences were found in this regard between ranibizumab monotherapy and combined with laser [32], and in a multicentric study comparing bevacizumab monotherapy versus combination with laser, bevacizumab showed better functional and anatomic results at 24 months than combination therapy [33].

Additionally, number of needed injections may be reduced by the adjuvant effect of laser treatment, as demonstrated by READ-2, RESTORE, and Protocol I studies. Small case series also found a reduced number of injections needed when combining laser with ranibizumab (mean of 2.4 versus 3.3 injections during a mean of 14 months of follow-up, resp.). This study also found that the mean duration between injections was significantly reduced in the combination therapy [34].

Newer technologies like imaged-guided photocoagulation systems and short-pulse lasers may improve laser outcomes. Combination therapy with bevacizumab injections, followed by navigated laser treatment applied after retinal thinning, required a mean of 4.4 injections during the 12 months of follow-up [35]. Likewise, combination therapy with short-pulse focal/grid photocoagulation required 3.4 ranibizumab injections in six months when no apparent microaneurysms were present, presumably because of a reduced influx of fluid into the treated macula [36].

Thus, although monotherapy macular laser treatment seems to have lost its role as a gold standard treatment for DME involving the center of the macula, it may still play an important role when combined with antiangiogenics helping to reduce macular thickness and number of injections needed.

Competing Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Clinical Study

Combination of Navigated Macular Laser Photocoagulation and Anti-VEGF Therapy: Precise Treatment for Macular Edema under Dry Retinal Conditions

Ernest V. Boiko[1,2,3] and Dmitrii S. Maltsev[3]

[1]*St. Petersburg Branch of the Academician S. Fyodorov IRTC "Eye Microsurgery", 21 Yaroslav Gashek St., Saint Petersburg 192283, Russia*
[2]*Department of Ophthalmology, Mechnikov North-West State Medical University, 47 Kirochnaya St., Saint Petersburg 191015, Russia*
[3]*Department of Ophthalmology, Military Medical Academy, 5 Klinicheskaya St., Saint Petersburg 194044, Russia*

Correspondence should be addressed to Dmitrii S. Maltsev; glaz.med@yandex.ru

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Purpose. To compare the controllability of navigated macular laser photocoagulation (MLP) in dry versus edematous retina and validate that pretreatment diagnostic images can be used as basis for navigated MLP after the macular edema (ME) has been resolved. *Materials and Methods*. Group 1 was divided into subgroup 1 (dry retina MLP) and subgroup 2 (MLP in ME) for comparisons of laser-burn diameters. In group 2, the areas and locations of ME before an intravitreal injection of anti-VEGF (IVAV) were compared with those of recurrent ME. *Results*. The average actual diameter as percentage of planned diameter of laser burn in subgroup 1 (11 DME eyes, 6 BRVO eyes) versus subgroup 2 (5 DME eyes, 8 BRVO eyes) was $115.1 \pm 9.1\%$ versus $167.2 \pm 13.8\%$ (based on retro-mode scanning laser ophthalmoscopy), and $118.1 \pm 14.8\%$ versus $176.1 \pm 11.6\%$ (based on OCT) ($p < 0.001$). In group 2 (6 DME eyes, 6 BRVO eyes), difference in mean ME area before IVAV and that in recurrent edema was insignificant ($p > 0.05$). *Conclusion*. The controllability of navigated MLP in dry retina is improved compared to edematous retina. This study validates that pretreatment diagnostic images can be used as basis for navigated MLP after the edema has been resolved.

1. Introduction

In diabetic macular edema, the combination of navigated macular laser photocoagulation (MLP) and antivascular endothelial growth factor (VEGF) therapy seems to reduce the number of injections needed with comparable good visual outcome as anti-VEGF monotherapy [1, 2]. In addition, MLP is indicated also for branch retinal vein occlusion (BRVO) without spontaneous resolution of macular edema [3–5].

MLP is performed in the regions of vascular leakage which are associated with retinal edema and thickening and are demonstrated by fluorescein angiography (FA) [6]. In recent years, optical coherence tomography (OCT) [7] and retro-mode scanning laser ophthalmoscopy (RM-SLO) [8] have been used to identify the retinal regions requiring photocoagulation. Unfortunately, in the presence of significant retinal edema and thickening, conventional MLP has substantial limitations due to difficulties in delivering precise amounts of laser energy to treatment areas.

Laser beam diffusion and difficulties with efficient visualization of laser burns due to thickened neurosensory retina may result in development of oversized laser burns and, consequently, excessive chorioretinal scars and imminent atrophic creep of the retinal pigment epithelium [9]. MLP would be performed more easily, with improved control by

the physician, if it could be preceded by either partial or complete resolution of macular edema (ME) with intravitreal anti-VEGF therapy or steroids. The use of MLP under dry retinal conditions requires, however, preliminary planning, because, after ME resolution, FA shows reduced or no regions of vascular leakage [10], whereas OCT shows reduced or normal retinal thickness [11].

Precise planning for MLP with the use of different methods for determining the boundary of retinal edema has become possible with the help of navigated technology. The latter involves superimposition of FA image, OCT thickness map, or RM-SLO image onto a color fundus photograph and placing laser spot marks at the regions of retinal vascular leakage, retinal thickening, or retinal edema [8, 12]. It is, however, unclear whether the area and location of recurrent retinal edema differ from those of pre-anti-VEGF treatment edema. Answering this question may help perform MLP in the most appropriate way under dry retinal conditions.

The purpose of this work was to compare the controllability of navigated MLP in dry versus edematous retina and validate that pretreatment diagnostic images can be used as base for navigated MLP after the edema has been resolved. The key indicator of MLP controllability was the comparison of (a) planned and actual laser burn diameters and (b) the laser power required for induction of laser burns in navigated MLP in the presence of macular edema with that after resolution of edema following treatment with a single intravitreal injection of anti-VEGF agents (IVAV). To validate the use of a pretreatment diagnostic image as base for navigated MLP, the area and location of ME before anti-VEGF were compared to those of recurrent ME after anti-VEGF when no laser had been used.

2. Materials and Methods

The study was approved by the Ethics Committee of Military Medical Academy and followed the tenets of the Declaration of Helsinki. Before treatment, patients were explained the cause of the disease and management options available to address macular edema, as well as advantages and disadvantages of these options. A management plan was agreed with each patient, and subsequent written informed consent was obtained for both participation in the study and for IVAV injection or MLP. Patients' decision in favor of having MLP (instead of anti-VEGF) as the first management stage was free, conscious, and voluntary.

This prospective study included patients with macular edema associated with diabetes (DME) or BRVO-related ME and not treated previously with MLP or anti-VEGF therapy.

There were two groups of patients. Group 1 (controllability analysis group) was used for comparisons (a) between the planned and actual laser burn diameters and (b) between the average laser power required for induction of laser burns in MLP in the presence of macular edema (subgroup 2) and that after resolution of edema following treatment with a single IVAV injection (subgroup 1). Group 2 was used for comparisons of the areas and locations of ME before anti-VEGF with those of recurrent ME after anti-VEGF (without MLP) (Figure 1).

Exclusion criteria included evidence of acute or chronic uveitis, vitreoretinal traction, fibrosis of the internal limiting membrane (with macular involvement), central RVO, or apparent optic media opacity (including cataract grades 2–4 on the Lens Opacity Classification System scale III [13]). An additional exclusion criterion for patients with branch RVO (BRVO) was duration of BRVO < 3 months. Ranibizumab injections (Lucentis) were administered to patients with DME (0.3 mg/0.05 cc) and to those with BRVO (0.5 mg/0.05 cc) of subgroup 1 and group 2, as per manufacturer's instructions.

2.1. MLP Controllability Analysis. At baseline, patients of group 1 (controllability analysis group) underwent RM-SLO and OCT.

The RM-SLO images obtained with SLO F-10 (NIDEK, Gamagori, Japan) were utilized for photocoagulation treatment planning and for measurements of actual diameters of laser burns after photocoagulation.

OCT retinal thickness maps (Enhanced Macular Map 5 (EMM5) protocol) were acquired on the spectral domain OCT system (RTVue-100, Optovue, Fremont, CA) and were used for determination of retinal thickness before MLP treatment planning. 3D reference scan pattern and line scan pattern were used for measurements of actual diameters of laser burns after MLP.

Navigated MLP was planned and performed using NAVILAS system (OD-OS GmbH, Berlin, Germany). The planning parameters used included a spot size of 100 μm, burn spacing of 2 burn-widths apart, and pulse duration of 100 ms (Figure 2).

Controllability was defined as the conformance between planned and actual diameters of laser burns, with the use of laser power required for the creation of barely visible (light gray) laser burns (as per Early Treatment Diabetic Retinopathy Study (ETDRS)) [6].

In subgroup 1 (dry retina MLP subgroup), MLP was guided by the pre-anti-VEGF RM-SLO and performed after complete resolution of ME following anti-VEGF treatment. Additional inclusion criteria for subgroup 2 were normal central subfield (CSF) retinal thickness values and no intraretinal cysts outside the CSF based on OCT data obtained after a single IVAV injection. After anti-VEGF treatment, eyes were examined on a weekly basis until the resolution of ME. If the requirements above were not achieved during 3 weeks after anti-VEGF treatment, the patient was excluded from the study; this resulted in the dropout of 62.3% of DME patients and 35.5% of BRVO patients. The intravitreal bevacizumab therapy was continued in patients who dropped out due to incomplete resolution of ME following a single injection.

In subgroup 2, MLP was planned and performed in the presence of edema without any preliminary therapeutic treatment.

2.2. Comparisons of the Areas and Locations of ME before Anti-VEGF Treatment with Those of Recurrent ME after Anti-VEGF Treatment. Additional inclusion criteria for group 2 were (1) no prestudy history of anti-VEGF treatment, (2)

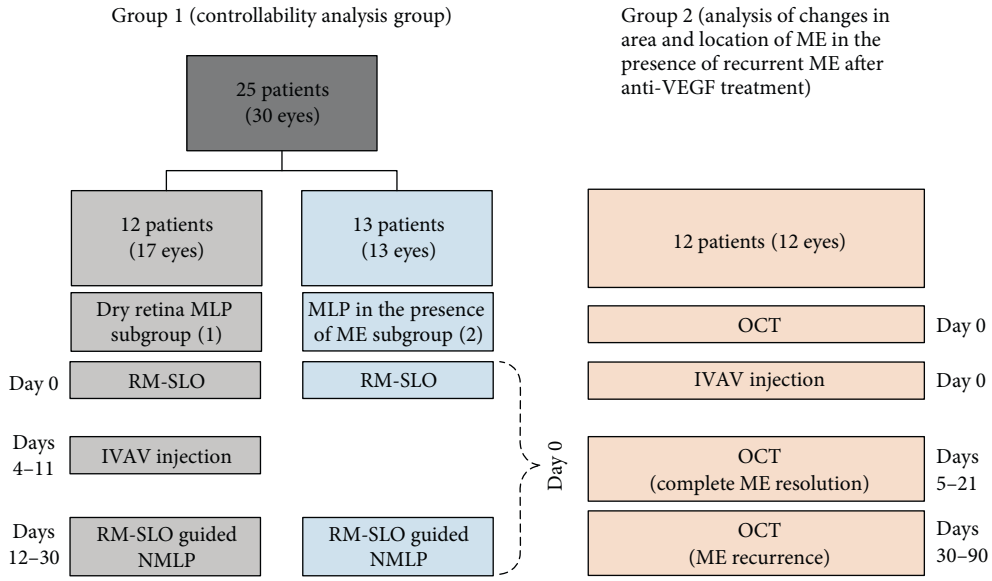

Figure 1: Schematic overview of the groups of the study.

normal CSF retinal thickness values based on OCT data obtained after a single IVAV injection, and (3) recurrent macular edema 1–3 months after a single IVAV injection.

OCT retinal thickness maps (EMM5 protocol) were used for comparisons of the areas and locations of ME before anti-VEGF treatment with those of recurrent (after anti-VEGF treatment) ME. RTVue-100 OCT software was used to quantitate the retinal area exceeding the threshold (350 μm) at full retina thickness maps and determine the area of macular edema. Full Thickness MM5 Significance Maps (related to the significance of the full retinal thickness deviation from normal) were used to compare the location of baseline edema with that of recurrent edema.

The ImageJ software (NIH, Bethesda, MD) was used to measure the area where the retinal thickness value was greater than the 99% confidence limit of normal thickness, both before anti-VEGF treatment and in recurrent ME. The area of overlap between these two areas was determined (Figure 3).

To investigate the degree of conformance between the planned and actual laser burn diameters, we determined the percentage of the ratio of average diameter of 10 laser-induced lesions visualized on RM-SLO (or OCT) 30 minutes after laser photocoagulation, to the planned diameter (100 μm). On OCT, the diameter of laser burn was determined at the outer nuclear retinal layer on the B scan crossing the center of this burn.

Average laser power was determined from the report provided by the Navilas laser system after completion of each laser application.

Statistical analysis was performed with Statistica 10.0 (Statsoft, Tulsa, OK). Unless otherwise stated, all the data are expressed as the means and standard deviation (SD). The Mann-Whitney U test was used to assess intersubgroup differences in age, actual diameter of laser-induced burns, and power required to induce a laser burn. A p level of 0.05 was considered statistically significant.

3. Results

3.1. MLP Controllability Analysis. Twenty-one Caucasian patients were included into group 1 (controllability analysis group), with 12 patients (17 eyes; 7 women and 5 men; mean age: 59.2 ± 11.5 years) in subgroup 1 (dry retina MLP subgroup) and 13 patients (13 eyes; 8 women and 5 men; mean age: 62.8 ± 12.6 years) in subgroup 2 (MLP in the presence of ME subgroup). The subgroups were not statistically significantly different in age (Table 1).

Based on RM-SLO data, average actual diameter as percentage of planned diameter of laser burn in subgroup 1 and subgroup 2 was 115.1 ± 9.1% and 167.2 ± 13.8%, respectively ($p < 0.001$). Based on OCT data, average actual diameter of laser burn in subgroup 1 and subgroup 2 was 118.1 ± 14.8% and 176.1 ± 11.6%, respectively ($p < 0.001$). The intermethod differences in measurements of actual diameter of laser burn were insignificant (Figure 4(a)). There were no statistically significant differences between DME patients and BRVO patients of each subgroup in average actual diameter of laser burns or average laser power ($p > 0.05$) (Table 2).

Eyes of subgroup 1 needed less average laser power than eyes of subgroup 2 (91.5 ± 12.3 mW and 112.8 ± 5.4 mW, resp., $p < 0.01$). In subgroup 2 (MLP in the presence of ME subgroup), the increase in actual diameter of laser burn resulted in decrease in burn spacing (Figures 4(b) and 5).

3.2. Comparisons of the Areas and Locations of ME before Anti-VEGF Treatment with Those of Recurrent ME after Anti-VEGF Treatment. Twelve patients (12 eyes; 7 women and 5 men; mean age: 64.2 ± 9.5 years) were included into

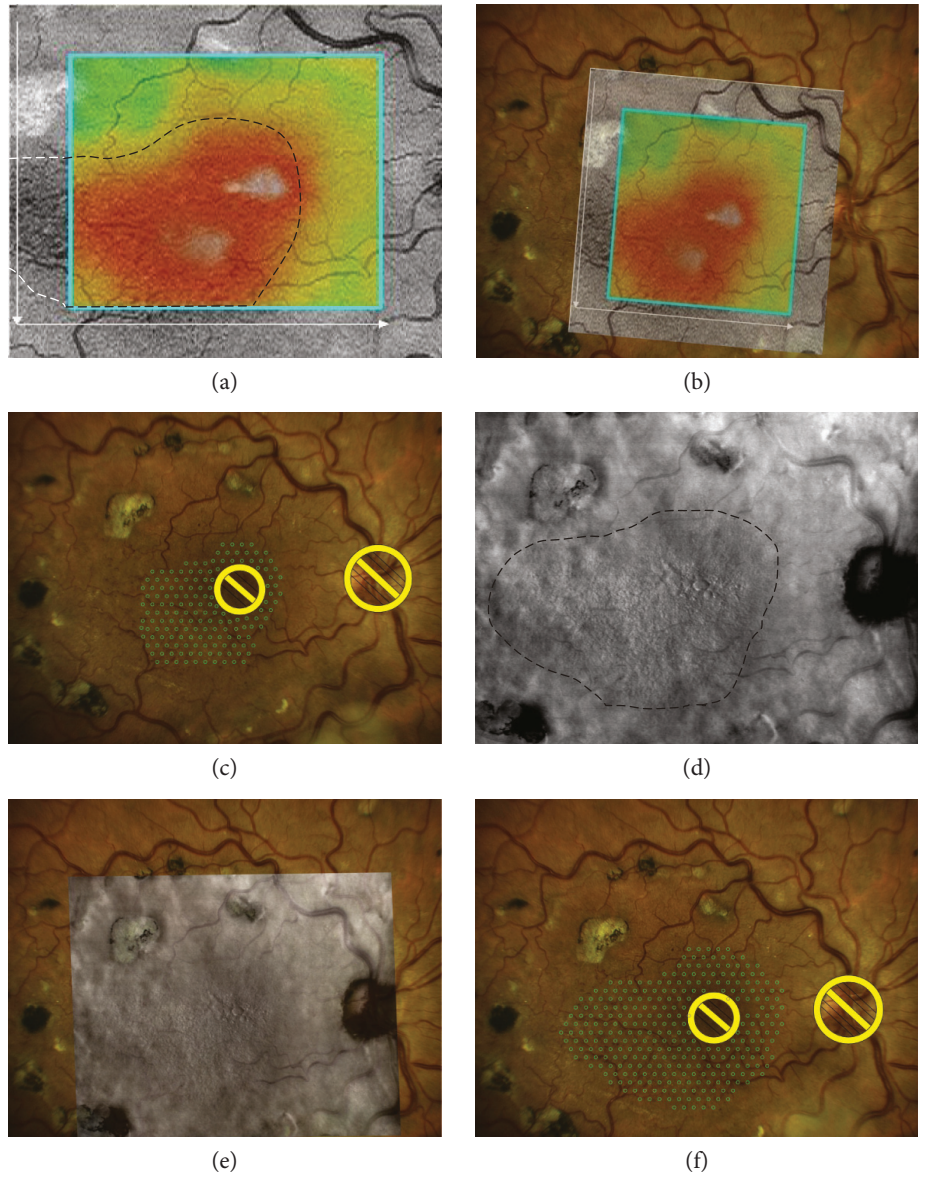

Figure 2: MLP planning based on OCT and RM-SLO. (a) OCT retinal thickness map demonstrates a thickened region (black dashed line) spreading outside the map boundary (white dashed line). (b) OCT map is superimposed onto the baseline image. (c) In OCT-guided planning for macular laser photocoagulation, the number of laser spot marks was 156. (d) RM-SLO image demonstrates a region of retinal edema with numerous microcysts. (e) RM-SLO image is superimposed onto the baseline image. (f) In RM-SLO-guided planning for macular laser photocoagulation, the number of laser spot marks was higher than in OCT-guided planning (259 versus 156).

group 2 (analysis of changes in area and location of ME in the presence of recurrent ME after anti-VEGF treatment). Diabetic ME and BRVO-related ME were found in 6 patients (6 eyes) and 6 patients (6 eyes), respectively, of this group.

The mean edema area before anti-VEGF treatment was $7.45 \pm 2.34\,mm^2$ and that in recurrent edema after anti-VEGF treatment was $7.15 \pm 2.18\,mm^2$ ($p > 0.05$) (Figure 6(a)). The mean length of time between anti-VEGF treatment and assessment of edema area in recurrent edema was 45.7 ± 21.9 days. The relative area of overlap between the total edema area before anti-VEGF and that in recurrent edema was $91.6 \pm 3.4\%$ (Figure 6(b)).

4. Discussion

This study demonstrates that MLP for DME or ME associated with BRVO can be performed with the help of navigated technology in the most precise manner (with the burns more uniform in diameter and in laser power required for their production) under dry retinal conditions, using a retinal macular thickness map obtained before anti-VEGF therapy.

It is known that the thinner the edema, the less laser power it needs in MLP, since accumulation of exudative fluid in macular edema results in reduced retinal clarity and altered penetration of laser radiation into outer retinal layers and into retinal pigment epithelium (RPE) due to power

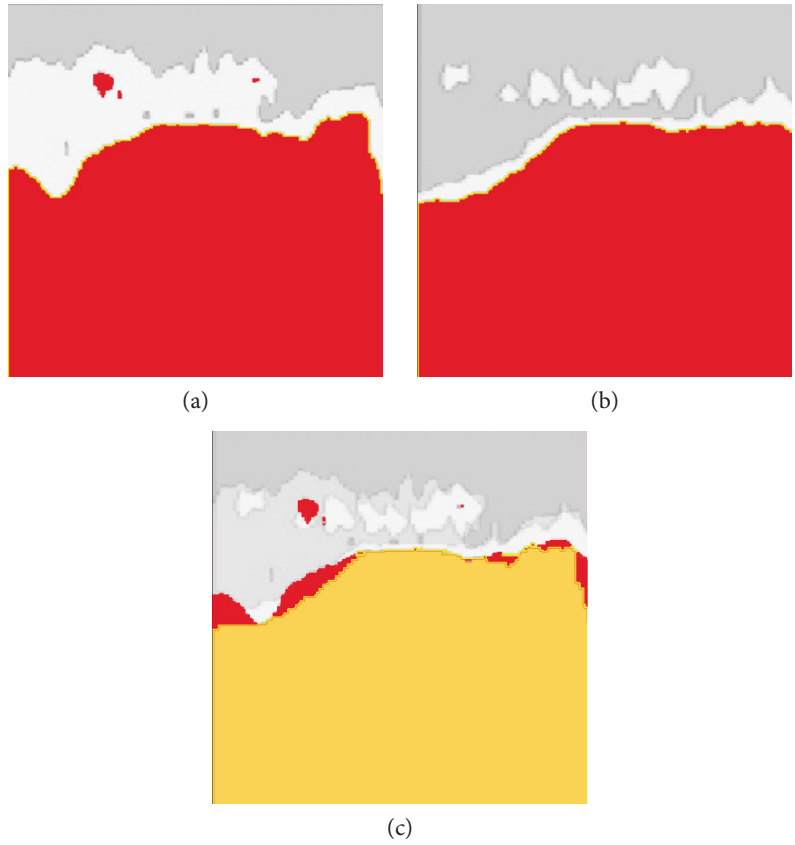

Figure 3: Typical example of the assessment of overlap between locations of initial and recurrent macular edema based on significance maps (related to retinal thickness deviation) in the patient with central retinal vein occlusion. (a) Location of macular edema before anti-VEGF treatment is marked with red. (b) Location of recurrent edema at day 41 after anti-VEGF treatment is marked with red. (c) Region of overlap between locations of initial macular edema and recurrent macular edema is marked with yellow. The region of nonoverlap is marked with red.

Table 1: Baseline characteristics of the sample.

	Group 1		Group 2
	Subgroup 1	Subgroup 2	
Mean age ± SD, years	59.2 ± 11.5	62.8 ± 12.6	64.2 ± 9.5
Gender (male, *n* (%))	5 (41.7%)	5 (38.5%)	7 (58.3%)
DME patients (eyes), *n*	6 (11)	5 (5)	6 (6)
BRVO patients (eyes), *n*	6 (6)	8 (8)	6 (6)
Mean BCVA ± SD	0.43 ± 0.19	0.21 ± 0.11	0.34 ± 0.15

BCVA: best corrected visual acuity; BRVO: branch retinal vein occlusion; DME: diabetic macular edema; SD: standard deviation.

dissipation. Therefore, conventional MLP with gray-white burns around the fovea may cause significant retinal damage in the macula. At the same time, according to ETDRS guidelines, the goal of grid treatment is to create barely visible (light-gray) burns, and absence of visible burns does not allow rating the laser treatment session as being performed adequately [6].

In the present study, we found that an increase by 15–20 mW in laser power was necessary to produce gray-whitish laser burns on retinas that were thickened due to retinal edema. This increase in laser power was found to result in a considerably enlarged size of laser burns at steady laser spot size (100 μm). The uncertainty regarding the resulting size of the laser burn may lead to unfavorable visual acuity or visual field outcome and decreases controllability of the MLP performed in the presence of a retinal edema. Our results go well along with previous studies that demonstrated a higher laser spot application accuracy focal MLP for DME [14] and a higher rate of accuracy in focal MLP treatment of DME than standard manual-technique laser treatment [15]. However, the concordance between the size of actual laser burns and that of planned laser burns has not been investigated until now, and this aspect of MLP controllability and accuracy is more important in grid MLP than in focal MLP due to a higher number of laser burns applied to the retina.

A number of studies have investigated visual outcomes following a combination of intravitreal anti-VEGF [16, 17] or steroid [18] injections with prompt or deferred MLP for macular edema. Although it is clear that intravitreal steroid therapy was performed for reduction of ME and as a pretreatment before MLP [16], no quantitative analysis of MLP controllability was performed, and no retinal assessment was performed on the presence and intensity of retinal edema (expressed as central retinal thickness) at the time of MLP. The use of MLP after resolution of ME will make it possible to avoid the problems of power titration which are associated with edema of the neuroepithelium and to

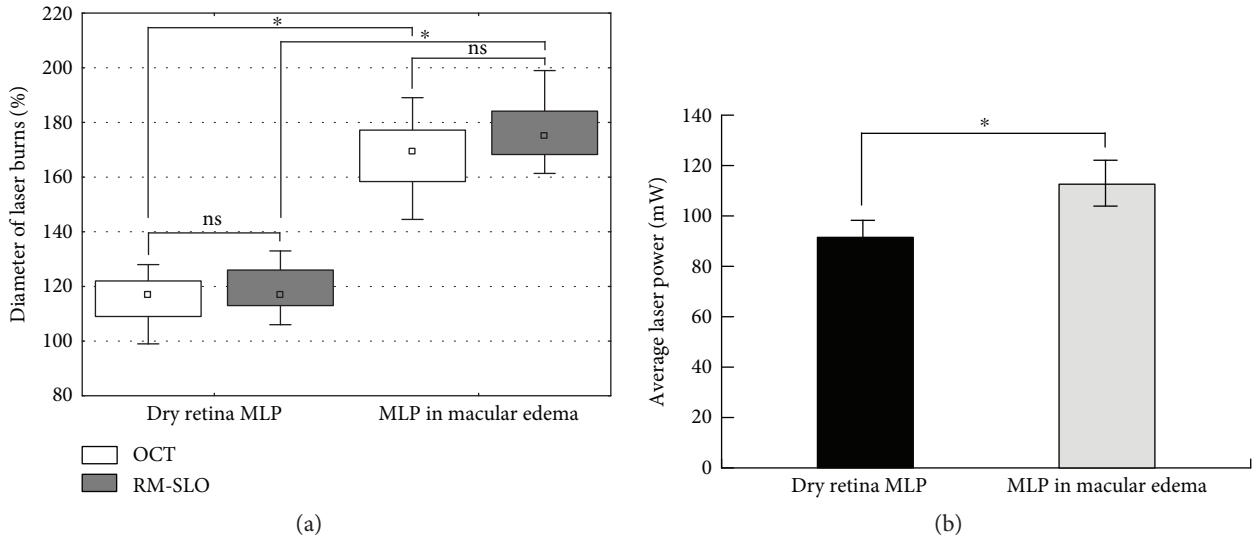

Figure 4: Comparison of the controllability of navigated MLP in dry versus edematous retina. (a) Difference in mean actual diameter of laser burns following navigated MLP in dry versus edematous retina based on RM-SLO (grey boxes) and OCT (white boxes) data. (b) Difference in average laser power for navigated MLP in dry versus edematous retina. $^{*}p < 0.05$; ns, nonsignificant.

Table 2: Comparison of diameter of laser burn and laser power in DME and BRVO patients.

		Subgroup 1		Subgroup 2	
		DME	BRVO	DME	BRVO
Mean diameter of laser burn ± SD, μm	OCT	112.8 ± 9.2	119.2 ± 8.0	164.8 ± 9.5	168.8 ± 10.2
	RM-SLO	117.9 ± 9.8	118.7 ± 7.1	175.6 ± 11.2	176.4 ± 12.6
Laser power, mW		90.2 ± 13.1	93.0 ± 13.4	111.3 ± 14.8	114.1 ± 16.2

BRVO: branch retinal vein occlusion; DME: diabetic macular edema; OCT: optical coherent tomography; RM-SLO: retro-mode scanning laser ophthalmoscopy; SD: standard deviation.

obtain laser-induced retinal burns of required size and spatial distribution.

RM-SLO is the technique which is important to use for accurate measurement of laser burns, since after the MLP performed in the presence of marked macular edema, burn boundaries are poorly defined on the fundus photographs, FA, and even OCT. This is due to the facts that (1) the physical principle used in RM-SLO allows detecting minor elevations of the RPE and medium interfaces (including the border between intact and coagulated retinal tissue) and (2) near-infrared laser radiation emitted by the SLO laser penetrates well through edematous retina. In the study presented here, RM-SLO-based and OCT-based measurements yielded comparable results regarding diameters of laser-induced burns, thus confirming the validity of these findings.

The use of the navigated approach to retinal photocoagulation under dry retinal conditions allows placing laser burns precisely in the locations where the areas of vascular leakage were revealed before anti-VEGF treatment (and where these areas will reappear in the recurrent edema) and avoiding excessive photocoagulation of relatively intact retina.

The use of pre-anti-VEGF edema maps seems reasonable, at least in the short term, since, after a single IVAV injection, the recurrent edema occurs, with its location and area being similar to those of initial edema.

In general, navigated photocoagulation under dry retinal conditions seems to be not only more controllable but also more standardized than conventional MLP.

The results of conventional MLP depend significantly on the intensity of retinal edema (expressed as CRT) and will differ from eye to eye as well as from one retinal subfield to another in the same eye. Theoretically, the problem of excessive actual burn size (compared to the planned one) can be solved for the MLP performed in the presence of edema by reduction of the laser spot size. However, this approach is significantly limited by poor visualization of laser burns and by the difference in edema intensities in different retinal subfields of the same eye. It is the conformance between planned and actual diameters of laser burns which is important for controllability of MLP, whichever diameter is preset. This may be ensured by pre-MLP intravitreal therapy (in particular, in the form of a series of injections) for resolution of edema. In addition, even a partial resolution of ME following IVAV injections may contribute to better MLP controllability, which is important for patients with ME persisting in spite of a series of injections. However, the methodology is not applicable in patients with ME resistant to anti-VEGF therapy. In

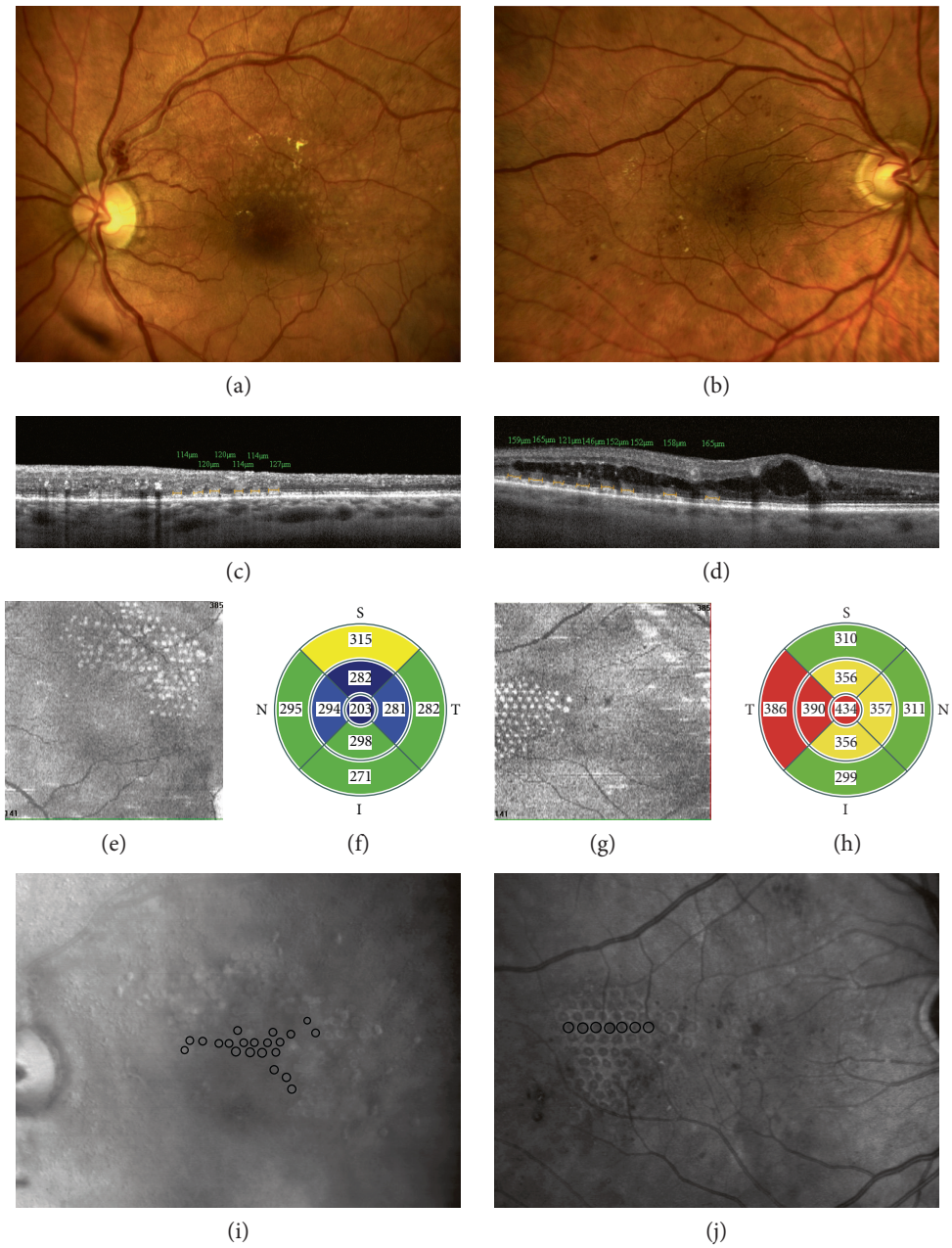

Figure 5: Example of difference in MLP controllability, for dry retinal conditions (subgroup 1) and for the presence of macular edema (subgroup 2). (a) Fundus photograph of the patient (subgroup 1), 30 minutes after MLP. (b) Fundus photograph of the patient (subgroup 2), 30 minutes after MLP. (c) B scan (through a photocoagulated region) of the patient of subgroup 1. (d) B scan (through a photocoagulated region) of the patient of subgroup 2. (e) En face image (at the level of the outer nuclear layer) of the patient of subgroup 1. (f) Retinal macular thickness map demonstrates either normal or decreased retinal thickness values in all ETDRS subfields in the patient of subgroup 1. (g) En face image (at the level of the outer nuclear layer) of the patient of subgroup 2. (h) Retinal macular thickness map demonstrates increased retinal thickness values in all ETDRS subfields in the patient of subgroup 2. (i) RM-SLO image of the patient (subgroup 1) 30 minutes after MLP. (j) RM-SLO image of the patient (subgroup 2) 30 minutes after MLP.

these cases, anti-VEGF therapy may be either prolonged or stopped and followed by vitrectomy.

The approach described may be also used for subthreshold micropulse laser photocoagulation, especially, for navigated micropulse MLP that has been recently approved for clinical use.

Our study has several limitations. First, the sample size was small (especially in MLP in the presence of ME subgroup) due to strict inclusion criteria followed in the study, as well as due to the fact that most of patients with ME receive intravitreal anti-VEGF therapy as the first therapy in the treatment schedule. Second, the dry retina MLP subgroup included only patients in whom edema resolved completely following a single IVAV injection, whereas patients in whom edema resolved incompletely were excluded. However, it may be also possible to perform MLP

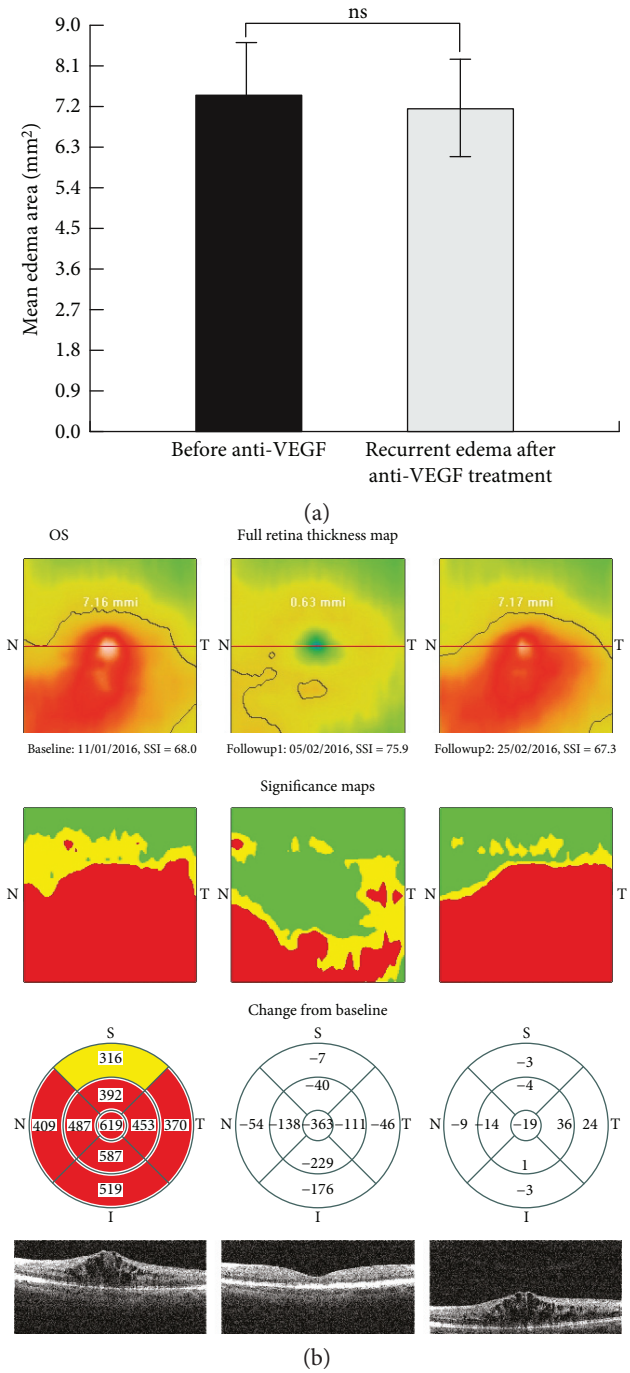

Figure 6: Comparison of the areas and locations of ME before anti-VEGF treatment with those of recurrent ME after anti-VEGF treatment. (a) Difference in mean edema area before anti-VEGF treatment and after ME recurrence. (b) Representative case of recurrent BRVO-related macular edema after a single anti-VEGF injection. Retinal thickness maps demonstrate that the area of recurrent edema was similar to that of edema before anti-VEGF injection. Significance maps demonstrate a near complete overlap between locations of initial edema (before anti-VEGF injection) and recurrent edema. ns, nonsignificant.

in the postedematous period if the number of IVAV injections required for complete resolution of edema is more than one. The requirement for additional data on the area and location of recurrent edema after a series of injections is one of the reasons why we did not investigate this possibility. It is possible that the area and location of recurrent edema after a series of injections will be different from those related to initial edema. Third, in this study, we did not assess functional differences in dry versus edematous retina following navigated MLP. It is well known that laser treatment combined with anti-VEGF results in better functional outcomes in diabetic or BRVO-related ME than does laser monotherapy; therefore, an appropriate comparison for functional outcomes would be to compare ME groups (or subgroups)

which received both laser and anti-VEGF. As, in our study, only patients of subgroup 1 received laser treatment combined with anti-VEGF, their functional outcomes should be definitely better than those in patients of subgroup 2. This is the major reason why we have not assessed final visual acuity or other functional outcomes in the study. Fourth, we did not examine late visual and anatomic outcomes. Assessing these outcomes will require a long follow-up, since the improvement after MLP increases slowly, and reduction in central retinal thickness after MLP in some studies has been observed for 2 years [18].

Although the benefits of combination treatment (MLP plus anti-VEGF therapy or intravitreal steroid) for macular edema has been postulated earlier [19], it is possible that "precise laser photocoagulation under dry retinal conditions" proposed will offer additional benefits.

In conclusion, the controllability of navigated MLP in dry retina is improved (with a better concordance between diameters of planned and actual laser burns, and less average power needed) compared to edematous retina. In addition, this study validates that pretreatment diagnostic images can be used as base for navigated MLP after the edema has been resolved.

Competing Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Research Article

Combination of Intravitreal Injection of Ranibizumab and Photocoagulation for the Treatment of Aggressive Posterior Retinopathy of Prematurity with Vitreous Hemorrhage

Yu Xu, Xiaoli Kang, Qi Zhang, Qiujing Huang, Jiao Lv, and Peiquan Zhao

Department of Ophthalmology, Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China

Correspondence should be addressed to Peiquan Zhao; zhaopeiquan@126.com

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To investigate the efficacy of intravitreal ranibizumab (IVR) combined with laser photocoagulation for aggressive posterior retinopathy of prematurity (AP-ROP) patients with vitreous hemorrhage, we conducted a retrospective observational case series study. A total of 37 eyes of 20 patients' medical records were reviewed. Patients first received IVR (0.25 mg/0.025 mL) and later photocoagulation. The mean postconceptual age of injection was 34.6 ± 1.4 weeks, and the mean follow-up period was 39.3 ± 8.3 weeks. During the follow-up, 96.6% eyes had various degree of rapid absorption of vitreous hemorrhage after IVR. The mean time of received first photocoagulation after IVR was 4.8 ± 2.9 weeks. Ten (27.0%) eyes received second laser therapy and the mean time of second laser therapy after IVR was 3.2 ± 0.8 weeks. All eyes exhibited adequate regression of ROP and were stable with attached retina. Fibrosis membrane was observed in seven eyes (18.9%) and three of them demonstrated mild ectopic macula. No significant side effects related to IVR were observed. So IVR could be conducted as primary treatment of AP-ROP associated with vitreous hemorrhage, which can improve the fundus visibility, followed by conventional photocoagulation. Further randomized controlled trials are necessary to compare the clinical efficacy and safety with conventional interventions.

1. Introduction

Retinopathy of prematurity (ROP), which is a major cause of visual impairment in children, is a vasoproliferative disorder associated with premature birth [1]. Laser photocoagulation is the gold standard treatment for proliferative ROP and has proven useful in reducing progression of classic ROP [2, 3]. However, in treating aggressive posterior retinopathy of prematurity (AP-ROP), as a more severe and unusual form of ROP, laser photocoagulation often fails to stop its progression to retinal detachment even with timely and complete treatment [4, 5]. Compared with classic ROP, AP-ROP is more likely associated with vitreous hemorrhage. The presence of vitreous hemorrhage often makes the completion of laser treatment more difficult due to the poor fundus visibility and is always associated with higher rates of unfavorable outcomes [4, 6, 7]. So how to treat these patients in a more efficacious way poses a real challenge to pediatric ophthalmologists.

Previous studies demonstrated that the vascular endothelial growth factor (VEGF) is a key factor in the progression of ROP [3]. Directly halting the VEGF molecules released from the ischemic retina, intravitreal injection of anti-VEGF agents, either with bevacizumab (Avastin®; Genentech Inc.) or Ranibizumab (Lucentis®; Novartis), was demonstrated as effective in treating severe ROP and thus gained increasing popularity [8–11]. Main advantages of anti-VEGF treatment over conventional laser photocoagulation include causing rapid regression of acute-phase ROP (neovascularization and plus disease), allowing potentials for retinal vascularization, approaching eyes with a rigid pupil, and reducing the risks of unfavorable outcomes in zone I or posterior zone II ROP [8, 9, 11].

Our purpose of this study was to investigate the efficacy of intravitreal injection of ranibizumab (IVR) combined with laser photocoagulation for the treatment of aggressive posterior retinopathy of prematurity (AP-ROP) patients with vitreous hemorrhage.

2. Methods

The design and execution of this retrospective noncomparative observational study was approved by Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine Institutional Review Board. The study protocol adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants' parents or guardians.

2.1. Patients. Thirty-seven eyes of twenty patients having a primary diagnosis of AP-ROP with vitreous hemorrhage obscuring the posterior pole or obscuring at least 4 contiguous clock hours of disease at the junction of vascular and avascular retina at Xinhua Hospital from April 2013 to March 2015 were enrolled. The medical records were carefully reviewed. AP-ROP patients without primary vitreous hemorrhage or with vitreous hemorrhage do not meet the above criteria, or the patients with incomplete contents of chart were excluded.

2.2. Diagnosis and Classification of ROP. The diagnosis of AP-ROP was according to the international classification of retinopathy of prematurity (ICROP, 2005) [12]. AP-ROP was defined as a flat network of neovascularization in posterior pole associated with increased dilation and tortuosity in all 4 quadrants. Zone I was defined as a circle with the radius that extends from the center of the optic disc to twice the distance from the center of the optic disc and the central macula. Posterior zone II was defined as a circle whose radius is three times the distance between the center of the optic disc and the center of the macula.

Persistent of ROP was defined as the lack of adequate regression of ROP. Recurrence was defined as arrest of anterior progression of retinal vasculature with new demarcation line, ridge, or extraretinal fibrovascular proliferation, with or without recurrence of plus disease [13].

2.3. Treatments and Follow-Ups. Infants were treated within 24 hours of diagnosis. The injection technique is described as follows. After the pupils were dilated with a combination of 0.5% tropicamide and 0.5% phenylephrine eye drops (Mydrin-P®, Santen Inc., Japan) the eyelids and conjunctiva were cleaned by 5% povidone iodine. A lid speculum was placed and an intravitreal injection with 0.25 mg/0.025 mL of ranibizumab was performed through pars plicata into the vitreous cavity with a 30-gauge needle inserted 1.0 mm posterior to the limbus of eyes under topical anesthesia with 0.5% proparacaine (Alcaine®, Alcon Laboratories Inc., USA). Vital signs were monitored throughout the entire procedure. The affected eye was given one drop of 0.3% ciprofloxacin 3 times a day for 5 days postoperatively. The patients were followed up at days 1, 2, 3, and 7 after IVR and then weekly until reaching 42 weeks postconceptual age (PCA).

In the cases exhibited with persistence/recurrence of ROP or peripheral retinal avascularity at PCA 42 weeks, treatment with laser photocoagulation was considered. All laser treatments were performed using an 810 nm diode laser (IRIS Medical Oculight SL 810 nm infrared laser; Iris Medical Inc., USA). Confluent laser burns, defined as laser burns less than half a burn width apart, were applied to the entire avascular retina. Repeated laser treatment to skip areas was carried out in one to two weeks after the primary laser treatment.

Then the treated patients were followed up at day 3, weekly or biweekly, or monthly to at least 24 weeks after retreatment. Extended follow-up was individually tailored according to response to treatment. Bilateral indirect ophthalmoscopy with scleral indentation was performed at each visit before and after treatment, and RetCam (Clarity Medical Systems, Pleasanton, CA, USA) wide-angle fundus imaging system was used to document fundus images of serial examinations.

3. Results

The demographic data of the patients are shown in Table 1. All these patients were transferred from outside hospitals. Among them, seventy-five percent (16/20) was male. The mean gestational age of these patients was 28.3 ± 1.6 weeks (range, 26–32 weeks) with the mean birth weight of 1221.3 ± 229.1 g (range, 900–1900 g). Four of the patients were from multiple birth pregnancies, and the remainder were singlets. All these patients had bronchopulmonary dysplasia, sepsis, and blood transfusions.

On the baseline, all the eyes had poor pupil dilation, and 91.9% (34/37) eyes demonstrated iris vascular engorgement. The mean PCA of patients who received IVR was 34.6 ± 1.4 weeks (range, 32–38 weeks). Of the 37 eyes, 33 (89.2%) eyes had zone I and 4 (10.8%) eyes had posterior zone II disease. Two (5.4%) eyes demonstrated extraretinal fibrovascular proliferation before the initial treatment (Figure 1).

On day 7 after IVR, the rigid pupil and iris vascular engorgement of all these eyes disappeared. Thirty-one (83.8%) eyes demonstrated significant absorption of vitreous hemorrhage and four (10.8%) eyes showed partial absorption of vitreous hemorrhage, while two (5.4%) eyes did not show any change of the vitreous hemorrhage. Thereby, the two eyes that had no change in vitreous hemorrhage were defined as persistent of ROP and received laser therapy immediately. Adequate regression of dilation and tortuosity of posterior vessels was observed in sixteen (43.2%) eyes, and subtle regression was observed in the remainder.

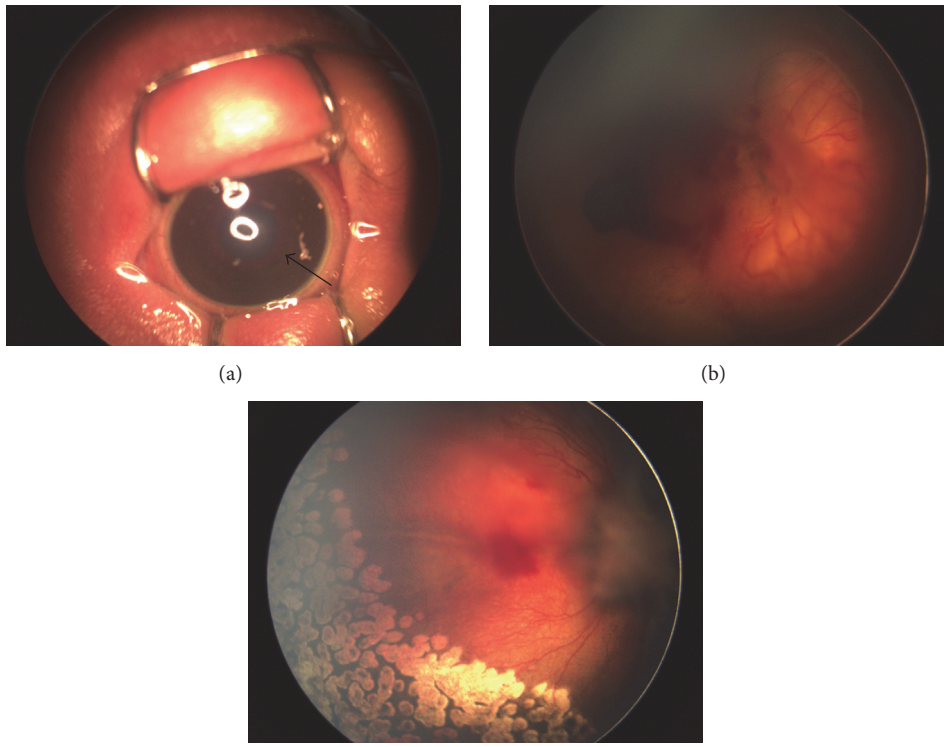
On day 14 after IVR, no obvious change was observed in vitreous hemorrhage, compared with day 7. Twenty (54.1%) eyes demonstrated adequate regression of dilation and tortuosity of posterior vessels. Thereby, the remaining 15 eyes having subtle regression of dilation and tortuosity of posterior vessels were defined as persistent of ROP, and received laser therapy within 48 hours.

Among 20 eyes that had adequate regression of ROP, 6 eyes showed various extent of continued vascularization of the peripheral retina after IVR treatment. But none of them had vascularized Zone III. New demarcation line was exhibited in 16 (80%) of these 20 eyes during the follow-up. The mean recurrence time after IVR was 7.1 ± 1.6 weeks (range, 4–10 weeks). At PCA 42 weeks, four (10.8%) eyes demonstrated persistent peripheral retinal avascularity without any new demarcation line. According to the protocol, we conducted laser therapy for these eyes.

Table 1: Characteristics of infants with AP-ROP associated with vitreous hemorrhage.

Patient number/eye	Gender	GA (weeks)	BW (g)	PCA (weeks), IVR	Zone before injection	Time after IVR (weeks), laser 1	Time after IVR (weeks), laser 2	Persistent ROP	Recurrence ROP
1 OD	M	27	1100	34	I	6			Y
1 OS				34	I	8			Y
2 OD	M	28	1090	35	I	2	3	Y	
2 OS				35	Posterior II	6			Y
3 OD	M	28	1400	33	Posterior II	7			Y
4 OD	M	28	1000	36	I	2	3	Y	
4 OS				36	I	2		Y	
5 OD	F	27	1250	34	I	7			
5 OS				34	I	7			Y
6 OD	M	28	900	36	I	2		Y	
6 OS				36	I	2		Y	
7 OD	M	28	1250	36	I	2		Y	
7 OS				36	I	2		Y	
8 OD	M	27	1125	33	I	9			
8 OS				33	I	9			
9 OD	M	31	1500	36	I	2	3	Y	
10 OD	M	32	1500	38	I	2	4	Y	
10 OS				38	I	2	4	Y	
11 OD	M	32	1900	36	I	2		Y	
11 OS				36	I	2		Y	
12 OD	M	27	1130	34	I	8			Y
12 OS				34	I	8			Y
13 OD	M	28	1010	34	I	6			Y
13 OS				34	I	6			Y
14 OS	M	29	1200	35	I	1	2	Y	
15 OD	F	26	950	32	Posterior II	10			Y
15 OS				32	Posterior II	10			Y
16 OD	M	28	1300	35	I	6			Y
16 OS				35	I	2	4	Y	
17 OD	F	28	1100	34	I	1	2	Y	
17 OS				34	I	4			Y
18 OD	M	27	1200	33	I	6			
18 OS				33	I	6			Y
19 OD	F	28	1300	34	I	2	4	Y	
19 OS				34	I	2	3	Y	
20 OD	M	29	1220	34	I	8			Y
20 OS				34	I	8			Y

AP-ROP: aggressive posterior retinopathy of prematurity; BW: birth weight; F: female; GA: gestational age; M: male; OD: right eye; OS: left eye; PCA: postconceptual age; Y: yes.



(a) (b) (c)

Figure 1: RetCam2 image of the right eye of patient number 17. (a) Anterior segment photography showing significant iris vascular engorgement (black arrow) and rigid pupil before IVR. (b) Before injection, fundus image showing prominent plus disease, vitreous hemorrhage, and fibrovascular proliferation at the posterior pole. (c) Fundus image 4 weeks after combination treatment of IVR and laser photocoagulation. An adequate regression of plus disease and significant absorption of vitreous hemorrhage was noted. A dense localized fibrous proliferation and mild ectopic macula was also noted.

Thus, all eyes received first laser photocoagulation therapy after IVR. The mean time of received laser therapy after IVR was 4.8 ± 2.9 weeks (range, 1–10 weeks). Ten (27.0%) eyes received second laser therapy according to our protocol. The mean time of patients who received second laser therapy after IVR was 3.2 ± 0.8 weeks (range, 2–4 weeks). After the combination of IVR and laser photocoagulation treatment, all eyes demonstrated adequate regression of ROP.

All patients were followed up for a minimum of 28 weeks. The mean follow-up time was 39.3 ± 8.3 weeks (range, 28–52 weeks). At the end of follow-up, seven (18.9%) eyes exhibited fibrosis membrane, three (8.1%) eyes demonstrated mild ectopic macula, and the remainder had normal vascular pattern of the posterior fundus. All eyes were stable with attached retina without any further surgical intervention. No other significant ocular or systemic adverse effects related to IVR were observed in these patients during the follow-ups.

4. Discussion

Our study demonstrated that intravitreal injection of ranibizumab combined with laser photocoagulation might be effective for AP-ROP associated with vitreous hemorrhage. All the rigid pupils and iris vascular engorgement disappeared, and 94.6% eyes showed various degrees of absorption of vitreous hemorrhage after IVR treatment, which can improve the fundus visibility and might contribute to operability of following conventional laser photocoagulation therapy. After the combination treatment, all eyes demonstrated adequate regression of ROP and 92% eyes had a favorite anatomical result.

With the improvement of neonatal intensive care, more and more very preterm infants can survive, leading to the increasing incidence of AP-ROP [1]. However, the prognosis of AP-ROP is poorer than that reported for zone II ROP, despite frequent screening in high risk infants and timely confluent laser photocoagulation [4, 14, 15]. Unfavorable outcomes for zone I ROP range from 28.6% to 55% [3, 14, 15]. For those AP-ROP associated with vitreous hemorrhage eyes, the prognosis would be even poorer. As the poor fundus visibility, complete retinal ablation is usually impossible and the retinopathy may continue to progress. Previous reports described that vitreous hemorrhage is the major risk factor for development of unfavorable outcomes. Sanghi et al. reported that hemorrhages before laser treatment is one of the most significant risk factors for retinal detachment in AP-ROP despite confluent laser photocoagulation [4]. Kim et al. concluded in their study that the presence of pretreatment hemorrhage increased the odds of developing a retinal detachment (RD) by a factor of 10, and presence of vitreous

organization increased the risk of RD by 16 times [6]. Therefore, the treatment options for these eyes are truly limited.

The purpose of laser photocoagulation is to reduce VEGF level produced by the avascular retina through ablating the periphery retina. Nowadays, anti-VEGF agents have been used as monotherapy or adjunctive therapy to laser photocoagulation, with effective results demonstrated [8–11, 16–19]. The majority of studies have reported the results of intravitreal injection of bevacizumab (IVB). There are a few studies that reported the results of IVR [10, 17, 18]. To the best of our knowledge, the present study is the first case series study about the treatment efficacy of combination of IVR and laser photocoagulation therapy in AP-ROP associated with vitreous hemorrhage patients.

In a recent retrospective research of 241 infants being followed up to over 65 weeks PCA, recurrence after IVB monotherapy for severe type 1 ROP was approximately 8.3% [20]. In another retrospective study, Yi et al. [18] treated 66 eyes of 33 premature infants diagnosed with type 1 ROP or AP-ROP with IVR as primary treatment. 87.9% eyes had total regression of ROP after a single injection. And 12.1% eyes had recurrence of ROP and received additional treatment. In our present study, only 54.1% eyes had adequate regression of ROP after the initial IVR treatment. The recurrence of ROP was observed in 43.2% (16/37) eyes, which is much higher than previous reports [8, 18, 20]. The reason of the lower rate of adequate regression and higher rate of recurrence of ROP after monotherapy of IVR in our study may probably be due to the fact that the patients we enrolled were more severe than other studies. But the recurrence time in our study ranged from 4 weeks to 10 weeks, which is quite similar to the other studies [18, 21]. Therefore, it seems that monotherapy of IVR is not sufficient in treating severe type ROP, such as AP-ROP associated with hemorrhage in particular. Close monitoring is important for early detection and timely retreatment of the recurrence of ROP and combination of laser photocoagulation therapy would be recommended.

An interesting finding is that, in our study group, 80% of patients were boys, indicating that boys may have predilection of severe ROP. However, we need to interpret this finding carefully. Our results might have been biased as the patients were all transferred from outside hospitals, and our sample size was small. They may not be able to represent the AP-ROP population. Although some previous studies reported that male gender is one of the predictors of treatment-requiring ROP [22, 23], we did not find any literature reporting the disparity in gender predilection to develop AP-ROP. Further prospective randomized studies may be needed to determine any gender predilection.

Safety is always of particular interest when considering the use of anti-VEGF agents in the treatment of infants, especially in our very vulnerable AP-ROP patients, as they are always associated with other systemic diseases and may still be in the process of organogenesis, in which VEGF still plays an essential role. Ranibizumab is an antibody fragment that has less molecular weight and better affinity to VEGF than bevacizumab [24]. This makes ranibizumab potentially more favorable in the treatment of infants with ROP with regard to efficacy and ocular and systemic safety profile. Recently, Wu et al. reported that serum VEGF levels in ROP patients were suppressed for two months after treatment with IVB, while VEGF levels were less affected after IVR treatment, which suggested that IVR could be a safer choice than IVB in the treatment of ROP [25]. In our present study, we did not observe any drug related systemic side effects during follow-up. But it remains important to be vigilant in the continued search for systemic complications and to conduct necessary clinical tests to identify any systemic complications.

On the other hand, the use of anti-VEGF agents for patients with ROP required attention to the risk of acute contraction of the proliferative membrane, thereby inducing or exacerbating RD. The development or progression of tractional RD is believed to be caused by a rapid neovascular involution with accelerated fibrosis and posterior hyaloid contraction, as a response to decreased levels of VEGF. There were a few case reports regarding progressive tractional RD after intravitreal injection of bevacizumab for ROP [26–28]. In our study, although seven eyes demonstrated fibrosis membrane, no patient had progressive fibrous traction after the injection.

Our study has several limitations worthy of consideration. The series is neither randomized nor prospective. The size of this cohort is relatively small, and all the data is from a single institution. Despite these limitations, the results suggest that combination of IVR and laser photocoagulation therapy can effectively treat AP-ROP with vitreous hemorrhage without additional vitreoretinal surgery and contributes to better anatomical results.

In conclusion, our study demonstrated that intravitreal injection of ranibizumab could be conducted as primary treatment of AP-ROP associated with vitreous hemorrhage, which can improve the fundus visibility, and followed by conventional laser photocoagulation therapy. Special attention must be paid to the risk of fibrous contraction and recurrence of ROP. Due to the limited case numbers, further randomized, prospective controlled trials are needed to determine the safety and definite efficacy and to improve our understanding of AP-ROP.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this article.

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Clinical Study

Subfoveal Choroidal Thickness after Panretinal Photocoagulation with Red and Green Laser in Bilateral Proliferative Diabetic Retinopathy Patients: Short Term Results

Ramak Roohipoor, Sina Dantism, Aliasghar Ahmadraji, Reza Karkhaneh, Mohammad Zarei, and Fariba Ghasemi

Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Science, Tehran, Iran

Correspondence should be addressed to Aliasghar Ahmadraji; hamidraji2000@yahoo.com

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Purpose. To compare subfoveal choroidal, central retinal, and peripapillary nerve fiber layer (RNFL) thickness after panretinal photocoagulation (PRP) with red and green laser in diabetic patients. *Study Design*. Randomized clinical trial. *Methods*. A total of 50 patients with bilateral proliferative diabetic retinopathy and no diabetic macular edema underwent PRP. One eye was randomly assigned to red or green laser. Subfoveal choroidal, central retinal, and RNFL thicknesses were evaluated at baseline and 6 weeks after treatment. *Results*. The mean subfoveal choroidal, central retinal, and peripapillary nerve fiber layer (RNFL) thickness increased significantly in each eye 6 weeks after PRP (P values in red laser group: <0.01, 0.03, and <0.01, resp., and in green laser group <0.01, <0.01, and <0.01). There was no difference between red and green laser considering subfoveal choroidal, central retinal, and peripapillary nerve fiber layer (RNFL) thickness increase after PRP (P values: 0.184, 0.404, and 0.726, resp.). *Conclusion*. Both red and green lasers increased mean subfoveal choroidal, central retinal, and peripapillary nerve fiber layer (RNFL) thickness significantly 6 weeks after PRP, but there is no difference between these two modalities in this regard.

1. Introduction

Diabetic retinopathy is one of the most common causes of visual loss worldwide. According to Early Treatment of Diabetic Retinopathy Study (ETDRS), protocol panretinal photocoagulation (PRP) can prevent severe visual loss in proliferative diabetic retinopathy (PDR) [1]. Several studies have shown histopathologic changes in choroid of diabetic patients [2–4]. Meanwhile, using panretinal photocoagulation (PRP), as was suggested beneficially by diabetic retinopathy study for proliferative diabetic retinopathy, has gotten general acceptance [1]. With the advent of enhanced depth imaging optical coherence tomography (EDI-OCT), it is now possible to visualize and measure choroidal changes easily.

Two different laser types for PRP are common, red and green laser. To the best of our knowledge, no other study has compared these two laser modalities in changing choroidal or central retinal thickness. In this study, we have evaluated the subfoveal choroidal, central retinal, and peripapillary retinal nerve fiber layer (RNFL) thickness changes before and after PRP using EDI-OCT and we compare the green and red laser in this regard.

2. Methods

This clinical trial was approved by the Institutional Review Board/Ethics Committee. Written informed consents were obtained from all participants. Eligible cases were 50 patients (100 eyes) with bilateral proliferative diabetic retinopathy. Exclusion criteria were advanced proliferative diabetic retinopathy, a history of any laser treatment (panretinal or focal laser photocoagulation), any history of intravitreal drug injection, ocular surgery, significant media opacity, myopia, or hyperopia with refractive error of more than 3 diopters.

Primary objective was to determine subfoveal choroidal and retinal thickness and peripapillary nerve fiber layer thickness changes 6 weeks after red versus PRP laser.

A complete ophthalmic examination including best corrected visual acuity (BCVA) using Snellen chart, Goldmann applanation tonometry, and dilated indirect ophthalmoscopy was conducted. Diabetic retinopathy grading (DRG) was performed according to the ETDRS definition [5]. Enhanced depth imaging optical coherence tomography (EDI-OCT) mapping was performed using SD-OCT (Spectralis®, Heidelberg Engineering, Heidelberg, Germany). All patients were treated on an outpatient basis. PRP was performed in 3 sessions with one week interval. A total number of 1600 to 2000 spots per eye were applied to ablate retina using Ellex Integre Pro Scan laser photocoagulator (82 Gilbert Street, Adelaide, SA 5000, Australia). The order of treated areas was as follows: nasal, inferior, superior, and then temporal retina. Time exposure was 100 milliseconds. To have threshold laser photocoagulation, power setting was chosen to have a mild gray-white burn (Grade 2) according to ETDRS guidelines [1]. Laser setting parameters did not differ significantly between two groups (mean power 303 mWatts in red and 290 mWatts in green laser group, P value: 0.14; mean laser spots 1789 spots in red and 1869 spots in green laser group, P value: 0.13).

One eye of all patients was randomly assigned to red laser and the other eye to green laser. Spectral domain optical coherence tomography images were obtained using Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) to measure central retinal thickness and enhanced depth imaging (EDI) mode to measure subfoveal choroidal thickness. BCVA measurement and an OCT scan were performed at baseline and 6 weeks after completion of PRP. Subfoveal choroidal thickness was measured using apparatus measurement tool at baseline and 6 weeks after PRP. Choroidal segmentation was done manually, moving the reference lines from the retinal borders to the choroidal borders. The internal limiting membrane line was moved to the base of the retinal pigment epithelium. The basement membrane line was moved to choriosclera junction. Also retinal nerve fiber layer (RNFL) thickness analysis was done at baseline and 6 weeks after treatment.

2.1. Statistical Analysis. Data were analyzed using SPSS software (version 16, SPSS, Inc.). Data normality was assessed using Shapiro-Wilk test. A paired sample t-test was used to compare macula and choroid thickness before and after treatment. Independent sample t-test was performed to compare macula and choroid thickness changes from baseline between two groups. General Linear Model was applied to assess differences within and between group. P values of <0.05 were considered significant.

3. Results

A total number of 50 patients with PDR entered the study. The mean age of the patients ± standard deviation was 55.6 ± 8.9 years. Nineteen patients were male (38%). The mean visual acuity of patients was 0.32 ± 0.28 logMAR and 0.27 ± 0.23 logMAR in red laser group and green laser group, respectively. The mean HbA1C was 8.47 ± 1.57%. The baseline characteristics of the patients are presented in Table 1. No complication occurred in both groups during laser and in follow-up period.

Table 1: Baseline characteristics.

Parameter	Statistics
Age	55.6 ± 8.9 years
Sex	38% male (19 patients), 62% female (31 patients)
HbA1C	8.47 ± 1.57%
VA	0.32 ± 0.28 logMAR in red group and 0.27 ± 0.23 logMAR in green group

The mean subfoveal CT increased significantly in each group at 6 weeks follow-up (in red laser group, 202.14 ± 24.5 micron at baseline and 211.7 ± 26.6 micron at 6 weeks, P value < 0.00, showing 4.86% CT increase compared to baseline) (in green group, 201.9 ± 21.13 micron at baseline and 208.9 ± 25.0 at 6 weeks, P value < 0.00, showing 3.54% increase compared to baseline) (Table 2).

There was not a significant difference between red and green laser in terms of choroidal thickness changes from baseline (P value 0.184).

In red laser group, the mean central retinal thickness was 271.6 ± 30.33 micron at baseline and 298.5 ± 62.14 micron at week 6 of follow-up (P value 0.03). In green laser group, the mean central retinal thickness was 267.0 ± 36.9 micron at baseline and 306.4 ± 73.3 micron at week 6 of follow-up, (P value 0.000 for both groups). There was no significant difference between macular thickness increase between two groups (P value: 0.404) (Table 2).

There was no significant association between choroidal thickness change and retinal thickness change in each group (P values: 0.051 and 0.52, resp.).

The mean peripapillary RNFL thickness was 100.5 ± 20.1 micron in red laser group at baseline which increased to 108.2 ± 23.1 micron at 6 weeks (P value 0.000) (7.8% as compared to baseline). In green laser group, it was 103.5 ± 19.8 micron at baseline which increased to 112.7 ± 22.9 in week 6 of follow-up (P value 0.000) (9.2% as compared to baseline). RNFL change between two groups was not significant (P value: 0.762) (Table 2).

4. Discussion

In this study, in eyes with proliferative diabetic retinopathy and without significant macular edema, the mean subfoveal choroidal, central retinal, and peripapillary RNFL thickness increased significantly after both red and green argon laser treatments.

This is in accordance with some of previously published studies that confirm this finding [6–9]. Takahashi et al. measured changes in choroidal blood flow in the foveal area one month after PRP in patients with severe diabetic retinopathy and no macular edema using a laser-Doppler flowmetry. They

Table 2: Measured thicknesses at baseline and week 6 of follow-up.

	Baseline	6 weeks	P value (within each group)	P value (between red and green laser group)
Subfoveal choroidal thickness (red laser group)	202.14 ± 24.5	211.7 ± 26.6	<0.000	0.184
Subfoveal choroidal thickness (green laser group)	201.9 ± 21.13	208.9 ± 25.0	<0.000	0.184
Central retinal thickness (red laser group)	271.6 ± 30.33	298.5 ± 62.14	0.03	0.404
Central retinal thickness (green laser group)	267.0 ± 36.9	306.4 ± 73.3	<0.000	0.404
RNFL thickness (red laser group)	100.5 ± 20.1	108.2 ± 23.1	<0.000	0.726
RNFL thickness (green laser group)	103.5 ± 19.	112.7 ± 22.9	<0.000	0.726

reported that PRP increases both the choroidal blood flow and the choroidal blood volume. Also, Cho et al. in their case series reported that PRP induced increases in both SFCT and macular thickness. Changes in subfoveal choroidal thickness did not correlate with changes in macular thickness in their study.

Two possible mechanisms are proposed by which this increase occurs. First, it has been attributed to redistribution of choroidal blood flow [10–14]. After PRP, following degradation of photoreceptors, blood flow of treated areas decreases. This leads to redistribution of blood in other untreated areas, especially the macula. Following blood flow increase, choroidal thickness increases in the macular area. This redistribution mechanism is documented in animals in some prior studies [10–17]. The second hypothesis is the inflammation triggered by PRP. This transient inflammation probably causes release of cytokines and leads to increase of blood flow and choroidal thickness [18, 19].

Mean CT increase in both groups in this study is similar to what have been reported before in other trials [7–10]. It is noteworthy that, in some other trials, the measured subfoveal CT showed decreased thickness after PRP in short term follow-up. They have hypothesized that the reason may be due to the destruction of choroidal vasculature after thermal damage of PRP [20, 21].

Also, we found that central macular thickness and RNFL thickness increased significantly in both groups; this is also similar to what has been found in other studies [20–24]. This finding is similar to what has been reported before about the increase of retinal thickness after PRP and it was attributed to the release of proinflammatory cytokines or hypoxia-induced macular edema [20–24].

Also, we did not find any correlation between changes of choroidal thickness and central retinal thickness. This is similar to what has been reported by Cho et al. [7].

One of the novel analyses done in this study is the comparison between red and green laser in changing retinal, choroidal, and RNFL thickness. Although all three measured variables showed significant increase after treatment in each eye, intereye comparisons were not statistically significant considering central retinal, subfoveal choroidal, and RNFL thickness changes (P values: 0.404, 0.184, and 0.762, resp.) that may indicate no considerable difference between red and green laser in this regard. To the best of our knowledge, there is only one report by Ghassemi et al. [24] that compared the difference between red and green laser in PDR patients. They reported significant increase of RNFL thickness after PRP without any difference between red and green laser. This is in accordance with our findings in this study.

One of the advantages of this study is selection of both eyes of one patient which can exclude the effect of systemic factors on retinal, choroidal, and RNFL thickness.

This study has some limitations including low sample size and short follow-up time. Nonetheless, this study showed significant increase of subfoveal choroidal, foveal retinal, and peripapillary RNFL thickness after red and green laser PRP and no significant difference between these two lasers in aforementioned measurements.

Disclosure

The sponsor or funding organization had no role in the design or conduct of this research.

Competing Interests

No competing interests exist for any author.

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