Journal of Ophthalmology

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Lead Guest Editor: Yoshihiro Takamura
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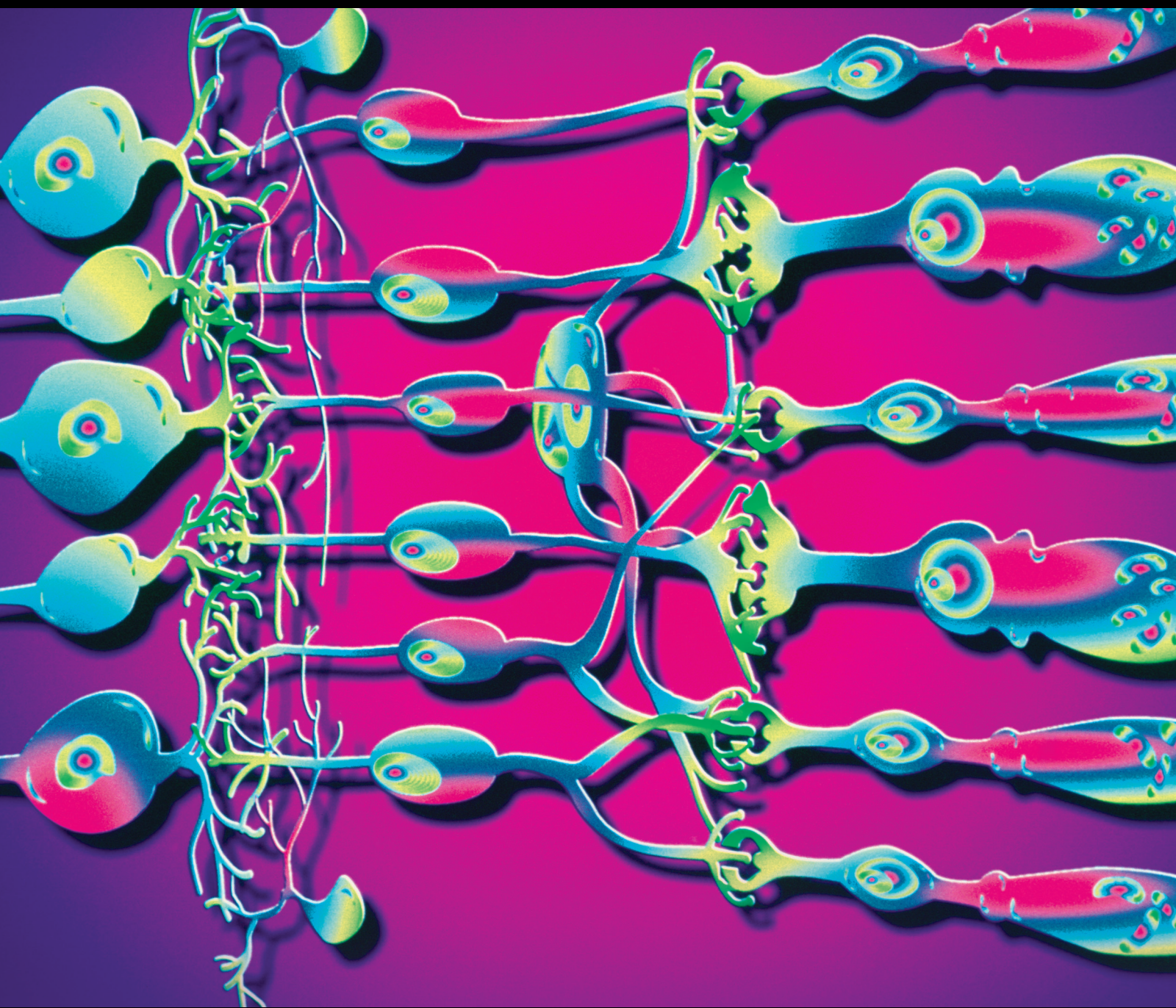

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Editorial Board

Contents

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Editorial

New Strategies for Treatment of Diabetic Macular Edema

Yoshihiro Takamura,[1] **Kishiko Ohkoshi**,[2] **and Toshinori Murata**[3]

[1]*Department of Ophthalmology, University of Fukui, Fukui, Japan*
[2]*Department of Ophthalmology, St. Luke's International Hospital, Tokyo, Japan*
[3]*Department of Ophthalmology, Shinshu University School of Medicine, Matsumoto, Japan*

Correspondence should be addressed to Yoshihiro Takamura; takamurayoshihiro@gmail.com

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Diabetic macular edema (DME) is the most frequent cause of vision loss in patients with diabetes and is an important public health problem. Recent randomized clinical trials have shown anti-vascular endothelial growth factor (VEGF) therapy improved visual acuity and macular swelling, and currently it has become the first line of the treatment of DME. However, the pathogenesis of DME is multifactorial, and several therapeutic modalities have been proposed for the treatment of DME. New strategy with the use of not only anti-VEGF drugs but also corticosteroids, laser photocoagulation, and vitrectomy can be alternative therapies for the persistent or refractory to anti-VEGF drugs. This special issue was intended to serve as a platform for sharing current data and new innovations in the management of DME.

Anti-VEGF drugs have become the gold standard for the treatment of DME, replacing macular laser photocoagulation. Best et al. showed the real-life efficacy of ranibizumab in DME at 12 months and the need for a large number of injections to achieve better visual outcomes. They also showed a trend to a lower compliance in diabetic versus neovascular age-related macular degeneration (nAMD) patients: only 16.8% of nAMD patients were lost to follow-up at one year versus 25.45% in diabetic patients. Many eyes respond well to anti-VEGF agents; nevertheless, some do not achieve favorable edema control, and these cases are referred to as refractory DME. Switching from one anti-VEGF drug to another is a viable first step for resistant DME management. Demircan et al. compared a switch group that comprised patients who were switched to aflibercept after showing a poor response to previous ranibizumab treatment with a ranibizumab group composed of patients who continued with ranibizumab injections despite the presence of poor response to this treatment. They showed that the switching therapy from intravitreal ranibizumab to aflibercept in persistent DME provided only morphologic improvement. The discrepancy between morphologic and functional outcomes may be explained by irreversible functional damage caused by long-standing DME.

Anti-VEGF treatment requires repeated intravitreous injections to maintain the therapeutic effect, and safety concerns regarding long-term systemic suppression of VEGF, which may increase a serious risk of cerebrovascular accidents, are emerging. Especially, type 2 diabetic patients with DME or PDR were associated with a 2-fold higher risk of fatal cardiovascular accidents compared with those without DME or PDR. Thus, a new optical treatment modality should be developed to improve the cost-effectiveness, safety, and visual outcomes. Predominantly focal leakage from microaneurysms (MAs) showed less response to anti-VEGF therapy. Focal laser treatment leads to the occlusion of MAs, pathologic vessels, or subretinal sites of leakage. The navigated laser photocoagulator has an eye-tracking laser delivery system and allows more accuracy for focal laser photocoagulation than conventional focal laser therapy for DME. Kato et al. showed that focal photocoagulation using Navilas 577+ aiming MAs, mainly localized outside of the perifoveal capillary network, was effective in treating DME with improvement in macular edema on OCT over 6 months. The navigated photocoagulation seems to demonstrate a higher laser spot application accuracy in focal laser therapy of DME than conventional laser technique. In their case series, indocyanine green angiography (ICGA) guide navigated laser was performed to most of the study eyes (84%). Indocyanine green dye is 98% bound to

lipoproteins in the blood. Thus, the dye hardly leaks, and ICGA defines the detailed retinal vascular abnormalities better than fluorescein angiography.

In addition to the accuracy, the less invasion of laser ablation in the retinal tissue is also clinically important. Although panretinal photocoagulation (PRP) is the standard therapy to inhibit the progression of diabetic retinopathy, PRP sometimes results in the worsening of macular edema. Recently developed short-pulse laser treatment is quicker, generates less heat, and is less painful to eyes than the conventional laser. Moreover, short-pulse laser treatment induces less inflammation, fewer up-regulation of inflammatory cytokines after PRP, and less macular thickening in patients with diabetic retinopathy than the conventional pulse duration. Higaki et al. demonstrated that fundus autofluorescence (FAF) images were useful to evaluate the changes in the photocoagulation scar sizes. The scars with the short-pulse laser showed lower expansion rates than those of the conventional laser. Analysis of FAF is an effective method to observe the functions of the retinal pigment epithelial (RPE) cells. Since retinal laser photocoagulation targets RPE, FAF analysis after laser photocoagulation may be an effective method to evaluate the RPE alterations and efficacy of laser photocoagulation.

Pars plana vitrectomy (PPV) is alternative strategy as a treatment for refractory DME. In the case of vitreoretinal interface abnormality, PPV can relieve the tractional component and can result in resolution of the edema. Vitrectomy may also contribute to a more efficient clearance of VEGF and other cytokines and better oxygen access from the anterior segment to the retina, thereby reducing DME. Hadi et al. showed the efficacy of subretinal balanced salt solution (BSS) injections in conjunction with conventional vitrectomy. Vitrectomy with the planned foveal detachment technique appears to be a promising solution for DME resistant to more than one anti-VEGF agent, intravitreal corticosteroids. The adjunctive therapy in the combination of the drugs with vitrectomy is also considered as a useful tool. Cui et al. compared the effect and safety of intravitreal injection of conbercept (IVC), ranibizumab (IVR), or triamcinolone acetonide (IVTA) on 23 gauge pars plana vitrectomy (PPV) for proliferative diabetic retinopathy. They showed that IVC and IVR could reduce the difficulty of the operation and improve the success rate of the surgery. In IVC and IVR groups, the fibrous membranes were easily separated from the retina with an individual of bleeding. Compared with IVTA group, IVC and IVR groups had more visual acuity gains after surgeries.

The guest editors appreciate the all authors of the papers submitted to this special issue. The editors also would thank the all reviewers, who devoted their energy and time and whose insightful comments and suggestions helped improve the manuscripts selected for this special issue. We hope that the readers of this special issue will find its contents interesting and clinically valuable.

Yoshihiro Takamura
Kishiko Ohkoshi
Toshinori Murata

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Clinical Study

Efficacy and Safety of Intravitreal Conbercept, Ranibizumab, and Triamcinolone on 23-Gauge Vitrectomy for Patients with Proliferative Diabetic Retinopathy

Jinglin Cui,[1,2] Hong Chen,[1] Hang Lu,[1] Fangtian Dong,[3] Dongmei Wei,[1] Yan Jiao,[2] Steve Charles,[4,5] Weikuan Gu,[2,6] and Lin Wang[1]

[1]*Center of Integrative Research, The First Hospital of Qiqihar City, Qiqihar, Heilongjiang 161005, China*
[2]*Department of Orthopedic Surgery and BME-Campbell Clinic, University of Tennessee Health Science Center, Memphis, TN 38163, USA*
[3]*Department of Ophthalmology, Peking Union Medical College Hospital, Beijing 100730, China*
[4]*Department of Ophthalmology, University of Tennessee Health Science Center, Memphis, TN 38163, USA*
[5]*Charles Retina Institute, Germantown, TN 38138, USA*
[6]*Research Service, Veterans Affairs Medical Center, 1030 Jefferson Avenue, Memphis, TN 38104, USA*

Correspondence should be addressed to Weikuan Gu; wgu@uthsc.edu and Lin Wang; Wanglinqsdyyy@126.com

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Introduction. To compare the effect and safety of intravitreal conbercept (IVC), intravitreal ranibizumab (IVR), or intravitreal triamcinolone acetonide (IVTA) injection on 23-gauge (23-G) pars plana vitrectomy (PPV) for proliferative diabetic retinopathy (PDR). *Methods*. Fifty patients (60 eyes) of varying degrees of PDR were randomly grouped into 3 groups (1 : 1 : 1) ($n = 20$ in each group). The 23-G PPV was performed with intravitreal conbercept or ranibizumab injection 3–7 days before surgery or intravitreal TA injection during surgery. The experiment was randomized controlled, with a noninferiority limit of five letters. Main outcome measures included BCVA, operation time, incidence of iatrogenic retinal breaks, endodiathermy rate, and silicone oil tamponade. *Results*. At 6 months after surgery, there were no significant differences of BCVA improvements, operation time, incidence of iatrogenic retinal breaks, endodiathermy rate, silicone oil tamponade, vitreous clear-up time, and the incidence of intraoperative bleeding between the IVC and IVR groups (all P values ≥ 0.05), but they were significantly different from the IVTA group (all P values < 0.05). IOP increases did not show significant differences between the IVC and IVR groups, but both were significantly different with the IVTA group. More patients had higher postoperative IOP in the IVTA group. *Conclusions*. The intravitreal injection of conbercept, ranibizumab, or TA for PDR had a significant different effect on outcomes of 23-G PPV surgery. Conbercept and ranibizumab can reduce difficulty of the operation, improve the success rate of PPV surgery, and decrease the incidence of postoperative complications.

1. Introduction

Proliferative diabetic retinopathy (PDR) is the leading cause of blindness among DR in diabetic patients [1–6]. PDR can lead to vitreous hemorrhage, traction detachment from fibrous proliferation, or neovascular glaucoma [7]. The current standard treatment for PDR is panretinal photocoagulation (PRP), combined with PPV whenever necessary. However, PRP is naturally destructive and has several potential adverse effects on visual function, including constriction of the peripheral visual field and reductions in night vision, contrast sensitivity, and color perception. Furthermore, it has been known that in the absence of intravitreal administration of ranibizumab or triamcinolone acetonide (TA), PRP can negatively affect vision and macular thickness in patients with diabetic macular edema (DME) [8]. In the surgery of advanced PDR, the occurrence of intraoperative hemorrhage when dissecting epiretinal

neovascular membrane will seriously affect visualization of the surgical field. In addition, repeated bleeding can prolong the operation time, increase the frequency of instrument exchange, and greatly increase the occurring rate of complications [9].

In order to reduce the chance of complications, a variety of drugs have been utilized in PPV for PDR. TA (Kenalog, Bristol-Myers Squibb Company, Princeton, NJ) (Kenakolt-A, Bristol Pharmaceuticals KK, Tokyo, Japan) is a water-insoluble steroid that inhibits various inflammatory reactions. It has been confirmed that it can aid visualization of transparent vitreous, reduce the degree of postoperative inflammation, and decrease the incidence of reoperation owing to epiretinal membrane formation in TA-assisted PPV for PDR [10–12]. In recent years, the important role of excessive release of vascular endothelial growth factor (VEGF) in many retinal vascular diseases has been unanimously recognized worldwide, including in PDR surgery [13–15]. Ranibizumab (Lucentis; Genentech Inc., South San Francisco, CA) and bevacizumab (Avastin; Genentech Inc., South San Francisco, CA) are monoclonal antibodies, militating by block VEGF-A. Studies showed that both of them can result superior visual acuity and central retinal thickness, reduce the duration of surgery, achieve fewer retinal breaks, and lessen intraoperative bleeding and also lead fewer endodiathermy applications [16]. However, bevacizumab has not been approved for use in intraocular injections in China. Conbercept (Langmu; Kanghong Inc., Sichuan, China) is a VEGF receptor (VEGFR) fusion protein. In late 2013, it received the new drug certificate, drug registration approval, and GMP certification from State Food and Drug Administration in China and has been widely used, accompanied by neovascularization vitreoretinopathy, such as neovascular age-related macular degeneration (AMD). It functions by competitively inhibiting the binding of VEGF with its receptor by blocking multiple targets, VEGF-A, VEGF-B, and placental insulin-like growth factor (PlGF) [17]. Most recently, conbercept has been reported to be an effective adjunct for the intravitreal conbercept (IVC) injection before vitrectomy for proliferative diabetic retinopathy (PDR) [18]. Thus, TA has traditionally been used PPV for PDR. Conbercept has been recently tested for its benefit when it was used PPV for PDR, mostly in Europe. Conbercept has been mostly tested in China. These three of them have never been directly compared. This study aims to compare the efficacy and safety of PPV when assisted by conbercept, ranibizumab, and TA intravitreal injection for PDR.

2. Methods

2.1. Study Population. This study adheres to the guidelines of the Declaration of Helsinki. The study was approved by the Institutional Review Board of the First Hospital of Qiqihar City. The protocol number is 2006-04. Patients' consents were given to all participants, and all patients signed the consents before participating the study. Between Jan 2015 and Dec 2015, 60 eyes from 53 patients were collected of varying degrees of PDR in the First Hospital of Qiqihar. There were 33 (55%) male and 27 (45%) female. The age was between 29 and 78 years old, with the average age of 58.83 (±3.62). Mean duration of DM was 26.57 ± 5.82 years. All patients had a history of DM, with 14 (23.3%) cases of type 1 DM and 46 (76.7%) cases of type 2 DM. Visual acuity was tested using Early Treatment Diabetic Retinopathy Study (ETDRS) charts at 4 m [18]. The BCVA was from HM to 20/80 as determined by protocol trial lens refraction. Other examinations included slit lamp directly, indirect ophthalmoscopy, IOP measurement, B-scan ultrasonography, fundus fluorescein angiography (FFA), and optical coherence tomography (OCT). Patients were selected for the PPV treatments (Table 1) based on the existence of extent of vitreous hemorrhage, retinal proliferation or traction retinal detachment, and other serious PDR. Exclusion criteria included those who received prior intravitreal injection, underwent vitreous or retinal surgeries, and glaucoma. Patients with abnormal blood coagulation indexes and other diseases of surgical contraindication were also excluded [19]. Before treatment, patients were provided with informed consent, the risks of surgery, and intraocular injection, and surgical complications related to the treatments were discussed. All patients understood the content and signed the informed consent. The study was approved by the First Hospital of Qiqihar Committees for Medical and Health Research.

2.2. Study Procedures. Patients were randomly divided into IVC, IVR, and IVTA groups (1 : 1 : 1) ($n = 20$ eyes in each group). Mean BCVA was 27.83 ± 6.78, 25.31 ± 4.23, and 28.46 ± 7.55 (ETDRS letters) in the IVC, IVR, and IVTA groups, respectively. The IVC group were 20 eyes in 17 patients, including 11 eyes (9 cases, 55%) of male and 9 eyes (8 cases, 45%) of female. Patients received 0.5 mg (0.05 ml, 10 mg/ml) intravitreal injections of conbercept [20] while the IVR group were 20 eyes of 20 patients, including 14 eyes (14 cases, 70%) of male and 6 eyes (6 cases, 30%) of female. Patients received 0.5 mg (0.05 ml, 10 mg/ml) intravitreal injections of ranibizumab [21]. PPV in both IVC and IVR groups was completed within 3–7 days after injection, and TA was not used during the surgery in both groups. The IVTA group were 20 eyes in 16 patients, including 12 eyes (11 cases, 60%) of male and 8 eyes (5 cases, 40%) of female. Patients received 4 mg (0.5 ml, 8 mg/ml) intravitreal injections of TA during the PPV [22]. The TA in the group of IVTA was removed during the surgery, with no remaining in the vitreum at the end of surgery. Three drugs were acquired commercially, and batch numbers for all vials used in the study were registered. Sterile techniques were used for every injection. Ophthalmic antibiotics and prophylactic peri-intravitreal injection were not used. Topical anesthetics were used (0.4% oxybuprocaine hydrochloride eye drops, Santen Pharmaceutical Co. Ltd.). The periocular skin, eyelids, and eyelashes were disinfected with 10% povidone-iodine swabs, and 5% povidone-iodine ophthalmic solution was applied to the ocular surface. All the patients received 23-G (Gauge) PPV (Alcon). The surgeries were performed by two experienced vitreoretinal specialist (Fangtian Dong and Hang Lu), who were masked from the patient information. The choice of tamponade was made between C3F8 gas or silicone oil depending on the difficulty and complexity of

Table 1: Baseline characteristics of participants with or without conbercept pretreatment.

	IVC ($n = 20$)	IVR ($n = 19$)	IVTA ($n = 19$)	P value
Sex				0.759
Male (eyes, %)	9 (11, 55%)	13 (13, 68.4%)	10 (11, 57.9%)	
Female (eyes, %)	8 (9, 45%)	6 (6, 31.6%)	5 (8, 42.1%)	
Age (yrs)				
Mean (SD)	60.74 ± 2.63	55.28 ± 5.16	57.49 ± 4.22	0.246
Type of diabetes (case, %)				0.527
1	3 (15.0)	4 (21.1)	2 (10.5)	
2	12 (6.0)	10 (52.6)	14 (73.7)	
Uncertain		5 (25.0)	5 (26.3)	3 (15.8)
Ocular profile (case, %)				
Study eye (left/right)	13/7 (65.0/35.0)	8/11 (42.1/57.9)	6/13 (31.6/68.4)	0.138
Previous history of laser	4 (20.0)	2 (10.5)	2 (10.5)	0.495
Lens status	3 (15.0)	4 (21.1)	2 (10.5)	0.663
Pathogeny (case, %)				
Nonclearing vitreous hemorrhage	9 (45.0)	9 (47.4)	8 (42.1)	0.914
Diffuse fibrovascular proliferation	4 (20.0)	3 (15.8)	5 (26.3)	0.125
Traction retinal detachment	7 (35.0)	7 (36.8)	6 (31.6)	0.573
Extent of vitreoretinal adhesion grade (case, %)				0.416
0	0 (0.0)	0 (0.0)	0 (0.0)	
1	2 (10.0)	4 (21.1)	5 (26.3)	
2	12 (60.0)	9 (47.4)	10 (52.6)	
3	6 (30.0)	6 (31.6)	4 (21.1)	
Duration of diabetes (y)				
Mean (SD)	24.25 ± 6.33	28.76 ± 5.27	25.98 ± 4.6	0.227
Mean BCVA (ETDRS letters)			0.531	
Mean (SD)	27.83 ± 6.78	25.31 ± 4.23	28.46 ± 7.55	
Snellen equivalent (range)	20/100–HM	20/100–20/2000	20/80–HM	
IOP (mmHg)				
Mean (SD)	15.24 ± 4.67	.64 ± 6.21	16.35 ± 2.89	0.395
Cardiovascular condition (case, %)	12 (60.0)	10 (52.6)	13 (68.4)	1.103
Hypertension (case, %)	15 (75.0)	11 (57.9)	14 (73.7)	0.587
Cerebral vascular disease (case, %)	5 (25.0)	7 (36.8)	4 (21.1)	0.862

the surgery, such as the severity of traction, size and number of retinal breaks or detachment, presence of iatrogenic breaks, retinectomy, severe bleeding, and other intraoperative complications [21]. Intraoperative panretinal endolaser photocoagulation was used, whenever necessary, at the end of the PPV surgery [23]. Ophthalmic antibiotics (5% levofloxacin eye drops, Santen, Japan) were used from the first day after surgery for 3 days, 4 times/d. Follow-up time was 6 months.

2.3. Data and Statistical Analysis. The primary outcomes were mean BCVA (ETDRS chart) monthly, operation time, incidence of iatrogenic retinal breaks, endodiathermy rate, and silicone oil tamponade. Secondary outcomes included average vitreous clearing time and the frequency of intraoperative and postoperative bleeding, PRP completion rate, reoperation probability, and intraocular pressure (IOP) in each group. Vitreous clearing time was defined as the interval between the end of surgery and the time at which the vitreous cleared up completely. Increased IOP was defined as an intraocular pressure > 21, which occurred within 24 hours after injections. To prevent effect of silicone oil on postoperative visual acuity, the final results of BCVA were determined after silicone oil removal. For patients with cataract after surgery, BCVA was measured after cataract extraction combined with intraocular lens implantation. Complications of cataract surgery were not included in this study.

The margin of clinical noninferiority was defined as five letters on the ETDRS visual acuity chart. Statistical analysis of the primary outcome variable, the mean change in BCVA from baseline to 6 m follow-up, was performed on data from the per protocol population (patients attending the 6 m visits). The mean scores of the primary outcome variables in three treatment groups were compared to each other using the independent samples t-test. The same statistical procedure was applied when analyzing the data according to the

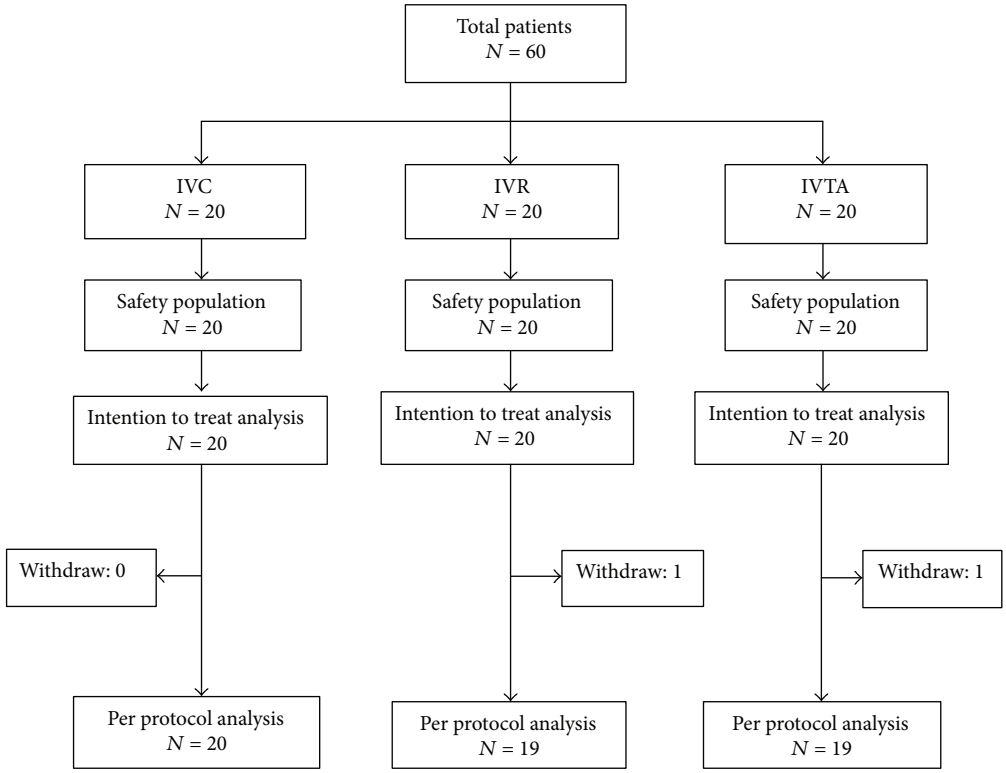

Figure 1: Study flow chart.

intent-to-treat principle, using multiple imputing to replace missing observations at 6 m follow-up.

Statistical analysis of secondary outcomes was performed only on data from the per protocol population, the operation time by independent samples t-test; if $p < 0.05$, the difference was considered statistically significant.

3. Results

3.1. Patients and Treatments. 60 patients were included in the treatment and safety analysis. The 6-month visits were completed by 58 (96.7%) patients (Supplementary Table 1). Two (3.3%) patients were lost to follow-up (one was in the IVR group and the other in the IVTA group). The primary analysis followed the intent-to-treat principle and included all randomized eyes (Figure 1). There were no substantial differences among the groups regarding age, sex, IOP, BCVA, and DR degree of severity in baseline characteristics (Table 1). To obtain 3 homogeneous groups of surgical complexity, we assigned scores from 0 to 3 for the following preoperative parameters: (1) vitreous hemorrhage (VH), (2) previous retinal laser photocoagulation, and (3) morphological types of retinal detachment, such as hammock, central diffuse, and table-top [24]. There was no significant difference in these scores. All patients did not receive PPV or intravitreal injection treatment, but some of them have received PRP treatment (cases were 4, 2, and 2 in 3 groups, resp.) (Table 2). The means and standard deviation of three groups showed that there was no difference among them.

3.2. Primary Outcomes. At the end of 6 m follow-up, the mean improvements in the IVC, IVR, and IVTA groups, respectively, were as follows (Figure 2): BCVA (ETDRS charts) was 25.10 ± 3.73, 26.32 ± 4.06, and 17.16 ± 2.87; the mean operation time was 56.65 ± 6.52, 54.89 ± 6.46, and 77.32 ± 6.36; the incidence of iatrogenic retinal breaks was 2 (10.0%), 2 (10.5%), and 8 (42.1%) cases; the endodiathermy rate was 5 (25.0%), 6 (31.6%), and 12 (63.2%) cases; and silicone oil tamponade was 9 (45.0%), 9 (47.4%), and 15 (78.9%) cases. There were no significant differences in BCVA improvements, operation time, incidence of iatrogenic retinal breaks, endodiathermy rate, and silicone oil tamponade between the IVC and IVR groups (all P values ≥ 0.05). However, each of these two groups showed significant difference with the IVTA group (all P values < 0.05) (Table 3).

3.3. Secondary Outcomes. The average vitreous clear-up time was 6.10 ± 1.52, 6.32 ± 1.57, and 11.11 ± 2.38 in the IVC, IVR, and IVTA groups, respectively (Figure 3); the incidence of intraoperative bleeding was 2 (10.0%), 3 (15.8%), and 9 (47.4%) cases in the three groups, respectively; postoperative bleeding was 1 (5.0%), 1 (5.3%), and 3 (15.8%) cases in the three groups, which occurred at 5 d, 1 w, and 1.5 m, respectively. Three patients required reoperation. Two cases were treated with Chinese drugs (He Xue Ming Mu Pian and Hong Hua Huang Se Su). BCVA was measured at 3 months after treatments. PRP completion rate was 11 (55.0%), 10 (52.6%), and 6 (31.6%) cases in the IVC, IVR, and IVTA groups, respectively. Four patients needed reoperation with the distribution of 1 (5.0%), 1 (5.3%), and 2 (10.5%) in the

Table 2: Baseline complexity surgery score of DR patients.

Surgery	IVC		IVR		IVTA	
	Cases ($n = 20$)	Complexity surgery Score	Cases ($n = 19$)	Complexity surgery Score	Cases ($n = 19$)	Complexity Score
VH						
Absent (0)	11	0	10	0	11	0
Mild (+1)	2	2	3	3	2	2
Moderate (+2)	5	10	4	8	5	10
Severe (+3)	2	6	2	6	1	3
Amount of previous						
Retinal photocoagulation						
Complete PRP (0)	1	0	0	0	0	0
Incomplete PRP (+1)	2	2	1	1	2	2
Focal (+2)	1	2	1	2	0	0
None (+3)	16	48	17			1
Configuration of retinal detachment						
Absent (0)	13	0	12	0	13	0
Hammock (+1)	4	4	3	3	2	2
Central diffuse (+2)	3	6	4	8	4	8
Table-top (+3)	0	0	0	0	0	0
Total complexity surgery score	20	80	19	82	19	78
Means (SD)		4.00 ± 13.38		4.32 ± 14.23		4.11 ± 14.39
P		0.67 (IVC versus IVTA)		0.39 (IVR versus IVTA)		

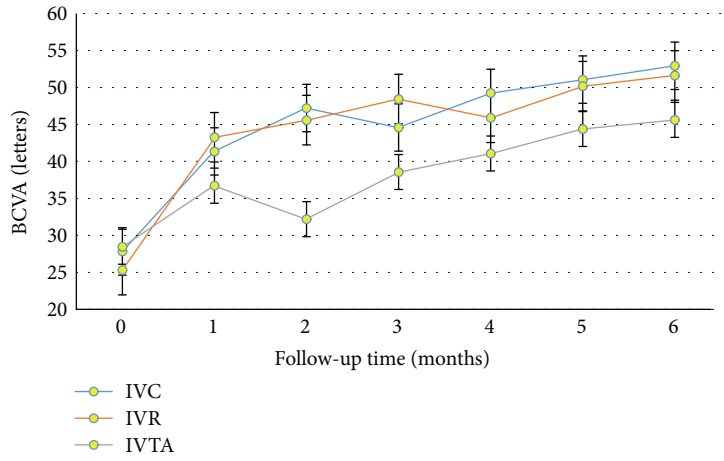

Figure 2: The mean changes in BCVA from baseline in IVC, IVR, and IVTA groups over 6 m were as indicated by the ETDRS chart letters. BCVA gradually increased after treatments in all three groups. The increases of BCVA were the most at the end of the first month. At the end of 6 m, the mean BCVA was improved by 25.10 ± 3.73, 26.32 ± 4.06, and 17.16 ± 2.87 letters in IVC, IVR, and IVTA groups, respectively (all P values < 0.05).

three groups, respectively. Three of them were caused by postoperative bleeding, and 1 was caused by silicone oil emulsified into the anterior chamber. There were no significant differences in vitreous clear-up time and the incidence of intraoperative bleeding between the IVC and IVR groups, while both of these groups were significantly different from the IVTA group. However, there were no significant differences in the incidence of postoperative bleeding, PRP completion rate, and reoperation probability among the 3 groups (Table 4).

3.4. Adverse Events. IOP increase is defined as an intraocular pressure > 25 mmHg, which appeared within 24 hours after injections. If IOP increased, subjects were monitored until intraocular pressure at 25 mmHg or less. The cases with increased IOP were 3 (15.0%), 2 (10.5%), and 9 (47.4%) in the IVC, IVR, and IVTA groups, respectively (Figure 4). There were no significant differences of IOP rate between the IVC and IVR groups, but both groups were significantly less than that in the IVTA group. Thus, more patients are at high IOP level in the IVTA group than

Table 3: Primary outcomes (Mean ± SD).

	IVC	IVR	IVTA	*P* value*
Mean BCVA improvement (ETDRS letters)				
(Mean ± SD)	25.10 ± 3.73	26.32 ± 4.06	17.16 ± 2.87	0.337, <0.01, <0.01
Operation time (minutes)				
(Mean ± SD)	56.65 ± 6.52	54.89 ± 6.46	77.32 ± 6.36	0.404, <0.01, <0.01
Incidence of iatrogenic retinal breaks (cases, %)	2 (10.0)	2 (10.5)	8 (42.1)	0.958, 0.024, 0.027
Endodiathermy rate (cases, %)	5 (25.0)	6 (31.6)	12 (63.2)	0.659, 0.014, 0.049
Silicone oil tamponade (cases, %)	9 (45.0)	9 (47.4)	15 (78.9)	0.885, 0.029, 0.045

*P value of IVC versus IVR, IVC versus IVTA, and IVR versus IVTA.

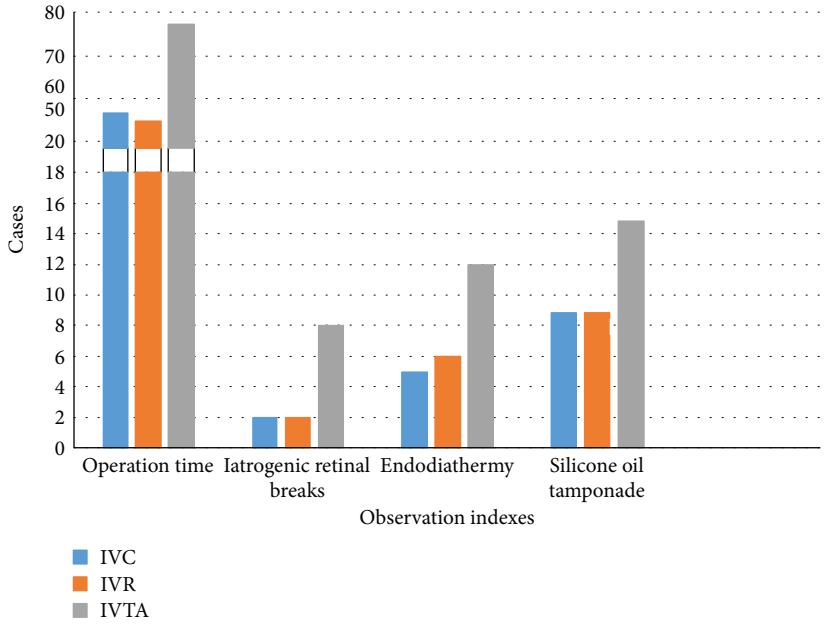

Figure 3: Comparison of outcomes of IVC, IVR, and IVTA groups at 6 m. There were no significant differences in operation time, incidence of iatrogenic retinal breaks, endodiathermy rate, and silicone oil tamponade between IVC and IVR groups. However, each of these two groups showed significant difference with the IVTA group.

Table 4: Secondary outcomes and IOP.

	IVC	IVR	IVTA	*P* value*
Vitreous clear-up time (days)				
(Mean ± SD)	6.10 ± 1.52	6.32 ± 1.57	11.11 ± 2.38	0.66, <0.01, <0.01
Intraoperative bleeding (cases, %)	2 (10.0)	3 (15.8)	9 (47.4)	0.602, 0.010, 0.04
Postoperative bleeding (cases, %)	1 (5.0)	1 (5.3)	3 (15.8)	0.971, 0.287, 0.305
PRP completion rate (cases, %)	11 (55.0)	10 (52.6)	6 (31.6)	0.886, 0.147, 0.199
Reoperation probability (cases, %)	1 (5.0)	1 (5.3)	2 (10.5)	0.971, 0.534, 0.560
IOP increase (case, %)	3 (15.0)	2 (10.5)	9 (47.4)	0.684, 0.031, 0.011

*P value of IVC versus IVR, IVC versus IVTA, and IVR versus IVTA.

the other two groups after surgeries. Among IOP patients, 5 were given anterior chamber tap, while others were treated with IOP-lowering drugs. The IOP of all of these patients decreased to normal ranges within 2 weeks. There were no significant differences in hypertension, cardiovascular, and cerebral vascular diseases among the 3 groups, compared with baselines (Table 5). No endophthalmitis, iris neovascularization, or TRD progression were observed during the follow-up period.

4. Discussion

PDR usually is extremely complicated with intraocular hemorrhage and TRD. Because of the existence of hemorrhage,

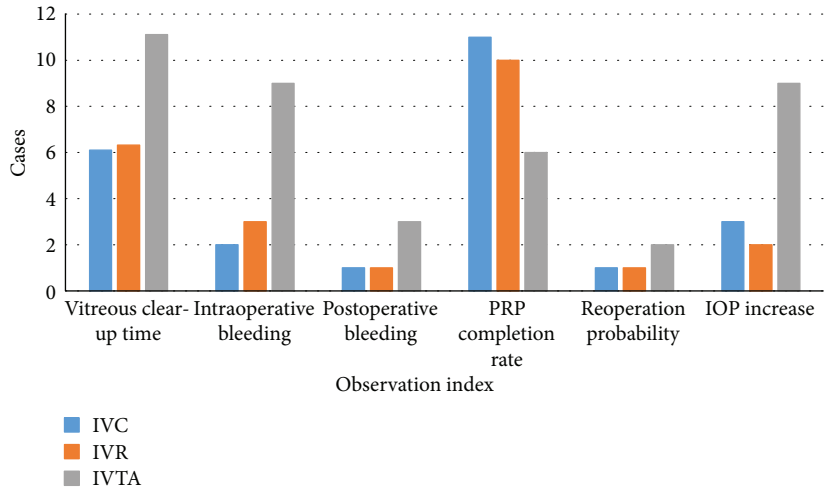

Figure 4: Secondary outcomes and adverse events of the IVC, IVR, and IVTA groups at 6 m. There were no significant differences in vitreous clear-up time and the incidence of intraoperative bleeding between IVC and IVR groups, while both of these groups were significantly different from IVTA group. More patients were at high IOP level in the IVTA group than the other two groups after surgeries. However, there were no statistically significant differences in the incidence of postoperative bleeding, PRP completion rate, and reoperation probability among 3 groups.

Table 5: System adverse events compared with baseline.

IVC	IVR	IVTA	*P* value*	
Cardiovascular disease (case, %)	14 (70.0)	13 (68.4)	14 (73.7)	0.519, 0.333, 0.729
Hypertension (case, %)	15 (75.0)	12 (63.2)	16 (84.2)	1.000, 0.748, 0.439
Cerebral vascular disease (case, %)	6 (30.0)	7 (36.8)	5 (26.3)	0.731, 1.000, 0.712

*P value of IVC, IVR, and IVTA.

exudation, and proliferation membrane during surgery in severe PDR, structures of retina are not easily identified and surgical difficulty and complexity are increased. Several studies have confirmed that VEGF plays a very important role in complex PDR [25, 26]. Due to long-term hypoxia in the occurrence and development of PDR, secretion of VEGF by retinal cells is increased, which causes new vessel hyperplasia, vitreous hemorrhage, and fibrovascular membranes and eventually leading to the TRD and severe damage to vision or even blindness [27, 28]. Clinical trials concluded that preoperative intravitreal injection of anti-VEGF drugs can reduce the intravitreal VEGF level, inhibit the activity of VEGF partially, and decrease retinal vascular leakage and neovascularization [29, 30]. Anti-VEGF drugs can also reduce the incidence of bleeding and iatrogenic holes during epiretinal membrane dissection [31, 32]. The VEGF family consists of VEGF-A, VEGF-B, VEGFC, VEGF-D, and placental growth factor (PIGF), which are related to receptors VEGFR-1, VEGFR-2, and VEGFR-3. VEGF-A can activate both VEGFR-1 and VEGFR-2. Meanwhile, VEGF-B and PIGF only bind to VEGFR-1. Also, VEGF-C and VEGF-D only bind to VEGFR-3 [33]. However, the monoclonal antibodies such as ranibizumab and bevacizumab had been found to bind VEGF-A only and lasted for only a short time [34]. Conbercept is a humanized soluble VEGFR protein which comprises extracellular domain 2 of VEGFR-1 and extracellular domains 3 and 4 of VEGFR-2, all of which are combined with the Fc region of human immunoglobulin G1 simultaneously. Based on its structure, it is predicted that it inhibits the binding of multiple VEGF receptors. Previous studies have demonstrated that extracellular domain 4 of VEGFR-2 can enhance the three-dimensional structure and efficiently advance dimerization [35]. Therefore, it is relatively stable and long lasting, in comparison with that of monoclonal antibodies. Also, preclinical studies have presented higher affinity of conbercept for VEGF than bevacizumab [36].

In addition, postoperative inflammation is also one of the major causes of postoperative complications, such as proliferative vitreoretinopathy (PVR). The postoperative inflammatory cells can secrete varieties of chemical mediators and cytokines, which stimulate the invasion of secondary inflammatory cells into the vitreoretinal tissue and activate the retinal glial cells and retinal pigment epithelium cells. These activated cells cause the proliferation of themselves, produce extracellular matrix, and contract the epiretinal membrane, thus leading to a secondary retinal detachment [37, 38]. Therefore, a reduction of postoperative inflammation is a logical strategy to prevent postoperative complications.

IVC, IVR, and IVTA are three commonly used procedures to improve the PDR operation in China. Only a single injection of TA was used early. Currently, anti-VEGF drugs in this study have been used in conjunction with PPV for PDR in China. Early studies showed that intravitreal

injection of TA successfully inhibited experimental PVR in the rabbit and optic disk neovascularization in the pig [39, 40]. In the study by Enaida et al., 62 Patients with PVR, diabetic macular edema (DME), PDR, rhegmatogenous retinal detachment (RRD), and macular hole retinal detachment (MHRD) were treated with TA-assisted PPV surgeries. Results showed that 49% of patients had improved vision and a lower incidence of reoperation caused by preretinal fibrous membrane formation [41]. Also, a study showed that performing intravitreal TA injection during PPV can increase the intraoperative visualization of vitreous; therefore, it may facilitate both removal of epiretinal membrane and separation of vitreous, especially in patients with undetached vitreous [42]. TA also was confirmed sufficient to reduce postoperative inflammation, as TA particles were left on the retinal surface for a few days [43]. Ranibizumab is a humanized monoclonal antibody fragment, which lacks an Fc domain, that functions by blocking all VEGF-A isoforms [44]. Conbercept is a different VEGFR fusion protein with multiple binding targets [45]. Large randomized controlled trials (RCTs) have authenticated principally the role of anti-VEGF agents in age-related macular degeneration, retinal vascular occlusion, and diabetic macular edema [46–49]. Studies in recent years have explored the role of anti-VEGF agents in PDR either as stand-alone therapy or as an adjunct to laser or PPV. Meta-analysis suggests that the addition of IVR to PRP results in improved structural and functional outcomes at 3 months/16 weeks and supports the assertion that application of intravitreal anti-VEGF therapy before PPV has the effect of reducing operating times, increasing the ease of surgery [50]. These facts support the use of anti-VEGF agents as adjunctive therapy in patients requiring PRP or vitrectomy for complicated PDR.

In our study, 60 eyes of PDR which combined with vitreous hemorrhage in different degrees and TRD were selected. Patients were randomly divided into three groups, ignoring the severity of the disease. The results showed that the preoperative application of intravitreal injections of conbercept and ranibizumab had equal effect in improvement of visual acuity, operation time, incidence of iatrogenic retinal breaks, endodiathermy rate, frequency of silicone oil tamponade, vitreous clearing time, and the incidence of intraoperative bleeding. Compared with the IVTA group, the IVC and IVR groups had more visual acuity gains after surgeries and increased operation safeties. In PPV surgery of the IVC and IVR groups, the fibrous proliferative membranes were easily separated from the retina with a few individual of bleeding. The advantages of the IVC and IVR groups are time saving for operations and reduced risks of surgical complications.

However, the posterior hyaloid can be clearly seen after the injection of TA suspension that enhanced visualization of vitreous in the IVTA group. Nevertheless, considering the potential increased risk of glaucoma and cataract associated with the use of intravitreal corticosteroids, the use of intravitreal corticosteroid preparations to reduce the likelihood of retinopathy worsening does not seem warranted [7].

Our data indicated that there were no significant differences among the three groups in the incidence of postoperative bleeding, PRP completion rate, and reoperation probability. Thus, although IVC, IVR, and IVTA may function in variable degrees, they all improved postoperative conditions and reduced complication occurrence of PPV. Conbercept, ranibizumab, and TA also improved the completion rate of postoperative PRP, prevented the development of DR, and greatly improved the patient's prognosis. The number of eyes with IOP increase was more in the IVTA group than the other two groups, suggesting that although TA was believed able to be removed from vitreous after PPV [40], its effect on IOP continually exists to a certain extent. There were no significant differences in other adverse events, such as hypertension, cardiovascular, and cerebral vascular diseases among the 3 groups compared with baselines, suggesting that there is very little or no influence on the system events from intravitreal injections of these three drugs. The early postoperative bleeding usually was relevant to the dissection of fibrovascular membranes in surgery which occurred typically within 1 week of surgery [51]. Pretreatment with conbercept surely facilitated the reducing of postoperative bleeding early after surgery due to the regression of neovascularization, cessation of hemorrhage from all potential bleeding sources, and reintegration of retinal vascular tissue. However, due to the short-time effect of anti-VEGF drugs injected before surgery, it did not affect late VH incidence [20]. Thus, due to the short duration of time of the anti-VEGF drug pretreatment in the eye, there were no significant differences in the incidence of postoperative bleeding among the three groups.

It has been controversial on the optimal timing of preoperative injection of anti-VEGF drugs before vitrectomy. In our study, PPV was completed during 3–7 days after intravitreal injection. Data indicated that drugs were effective and patient postoperative conditions were significantly improved. Furthermore, no significant development of proliferative lesions was observed in 6 m. Since the blood glucose level is one of the important factors that affect the development of PDR [52], in our study, all patients were asked to actively control blood glucose before and after surgeries, preventing hyperglycemia leading to surgical failure. Several studies reported that drugs caused the retinal pigment epithelium (RPE) tears [53, 54]. However, in our study, no RPE tears were found after intravitreal injection during follow-up. Since there are many factors in the formation of cataract, for example, silicone oil intraocular filling can also lead to cataract, our study did not include cataract as one of the surgical complication [7].

In conclusion, this study suggested that in a developing country such as China, PDR patients living in rural areas usually could not receive early and effective treatment due to inconvenient transportation and inadequate community health care services; therefore, it is essential to reduce the cost of surgical complications, reoperation, and long-term treatment. 23-G PPV surgery assisted by intravitreal injection of conbercept, ranibizumab, or TA for PDR had a significant impact on patient health condition and economic burden. The application of these drugs can reduce difficulty of the operation, improve the success rate of PPV surgery, and decrease the incidence of postoperative complications,

therefore reducing the patient's economic burden in China. Conbercept and ranibizumab have equal effectiveness and achieved better results than TA. The safety and efficacy of the anti-VEGF drugs were confirmed in the treatment of complex PDR. However, our research is limited, as the observation time is short, the long-term effects and complications of drugs had not been well reflected. Function mechanism of these drugs is also not completely understood. In addition, the number of cases in this study is inadequate for a definitive conclusion. Therefore, these results also need to be proved by clinical trials of large sample sizes and extended follow-up period.

Ethical Approval

This study was approved by the Institutional Review Board and Ethics Committee of the First Hospital of Qiqihar City.

Disclosure

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

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

Jinglin Cui, Weikuan Gu, and Hong Chen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Jinglin Cui, Lin Wang, Weikuan Gu, and Hong Chen were responsible for the study concept and design. Jinglin Cui, Hang Lu, and Fangtian Dong performed the clinical treatment and data collection. All authors performed the acquisition, analysis, or interpretation of data. Jinglin Cui, Weikuan Gu, and Steve Charles were responsible for the drafting of the manuscript. All authors helped in the critical revision of the manuscript for important intellectual content. Jinglin Cui, Yan Jiao, and Weikuan Gu performed the statistical analysis. Jinglin Cui, Lin Wang, Dongmei Wei, and Weikuan Gu performed the literature search. Yan Jiao, LinWang, Weikuan Gu, Steve Charles, and Hong Chen obtained funding. Lin Wang, Dongmei Wei, Hang Lu, and HongChen were responsible for administrative, technical, or material support. Hong Chen, Lin Wang, and Dongmei Wei supervised the study.

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Supplementary Materials

Supplementary Table 1: detailed disease phenotypes of individual eye in three groups. *(Supplementary Materials)*

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Clinical Study

Evaluation of Vitrectomy with Planned Foveal Detachment as Surgical Treatment for Refractory Diabetic Macular Edema with or without Vitreomacular Interface Abnormality

Ahmed M. Abdel Hadi

Ophthalmology, Faculty of Medicine, Alexandria University, Alexandria, Egypt

Correspondence should be addressed to Ahmed M. Abdel Hadi; aabdelhadi2010@gmail.com

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Purpose. To evaluate the therapeutic efficacy of subretinal BSS injections done during vitrectomy for refractory diabetic macular edema (DME) resistant to other modes of treatment including previous vitrectomy. *Materials and Methods*. A prospective, interventional noncomparative case series in which cases had refractory DME with a central macular thickness (CMT) $\geq 300\,\mu$m, despite previous anti-VEGF therapy (ranibizumab or bevacizumab with shifting to aflibercept). Some cases even received intravitreal triamcinolone acetonide injection, before attempting this solution. The study included group 1, surgically naïve eyes, and group 2, cases with persistent edema despite a previous vitrectomy (7 eyes (25%)). The cases were also divided into group a, eyes with normal vitreomacular interface, and group b, with abnormal vitreomacular attachment (VMA) (6 (21.4%)). The 1ry endpoint for this study was the change in CMT after 9–12 months from surgery. The 2ry endpoints were change in BCVA, recurrence of DME, and surgical complications. *Results*. The study included 28 eyes, 6 (21.4%) of which suffered from edema recurrence. The mean recorded CMT was $496 \pm 88.7\,\mu$m and $274.1 \pm 31.6\,\mu$m preoperatively and postoperatively, respectively. In all eyes, the preoperative mean BCVA in decimal form was 0.2 ± 0.11, which improved significantly to 0.45 ± 0.2. In the end, the CMT of groups 1 and 2 measured $239\,\mu$m and $170.8\,\mu$m, respectively ($p = 0.019$). The preoperative BCVA in groups 1 and 2 was 0.16 ± 0.07 and 0.37 ± 0.14, respectively, which improved to a mean of 0.34 ± 0.09 and 0.7 ± 0.16 postoperatively, respectively ($p = 0.185$). *Conclusion*. Vitrectomy with a planned foveal detachment technique was shown to be a promising solution for refractory DME cases with rapid edema resolution. CMT was shown to improve more in eyes where conventional vitrectomy was not attempted. Moreover, cases with VMA resistant to pharmacotherapy was shown to respond well to this technique. The study has been registered in Contact ClinicalTrials.gov PRS Identifier: NCT03345056.

1. Introduction

Many therapeutic options exist for diabetic macular edema (DME)—the leading cause of visual diminution in patients with diabetic retinopathy (DR). Since 2010, antivascular endothelial growth factors (anti-VEGF) have become the gold standard for DME treatment, replacing macular laser photocoagulation [1, 2].

Many eyes respond favorably to anti-VEGF agents; nevertheless, some do not achieve optimal edema control, and this group is referred to as refractory DME. The prevalence of refractory DME is estimated to be up to 50% [1], constituting a large unmet defect in DME management. Switching from one anti-VEGF agent to another is a viable first step for resistant DME management [3]. In addition, corticosteroids are considered by many researchers as the main therapy for DME refractory to anti-VEGF treatment, due to their multimodal actions [4]. Despite these strategies, resistant DME cases still exist.

Surgery is thought to play a role in nontractional cases, allowing a more efficient clearance of VEGF and other cytokines from the retina and allowing a better oxygen access from the anterior segment to the retina, thereby reducing DME [5]. In addition, the presence of a vitreoretinal interface

abnormality (VRA) reduces the therapeutic effect of anti-VEGF agents in patients with DME. These agents may alter the balance between angiogenic and fibrotic growth factors in patients with diabetic retinopathy, termed the angiofibrotic switch, which can result in increased retinal traction in some patients with proliferative diabetic retinopathy (PDR) prior to surgery [6]. Vitrectomy can relieve this tractional component and can result in resolution of the edema [7].

Improvement of the condition of the retina after vitrectomy takes time, and during that time, the photoreceptor cells may become permanently damaged [8–11] by the chronic macular edema leading to poor visual prognosis [12]. Furthermore, recent optical coherence tomography (OCT) observations show that a shorter time from the onset of DME to its resolution is the major factor affecting the integrity of the ellipsoid zone and a good visual outcome [13, 14], indicating the importance of rapid resolution of DME after vitrectomy.

Morizane et al. evaluated the therapeutic efficacy of subretinal balanced salt solution (BSS) injections in conjunction with conventional vitrectomy for treating diffuse DME. They demonstrated that this technique is effective for rapid resolution of diffuse DME resistant to anti-VEGF therapy and for the improvement of visual acuity [15]. Their study did not evaluate the usefulness of this technique in cases with vitreomacular interface abnormality resistant to intravitreal pharmacotherapy. Intravitreal corticosteroids were also not tried in their cohort of resistant cases, because various methods for administering steroids, including dexamethasone intravitreal implants, were not approved in Japan at the time. Therefore, they used sub-Tenon injection of triamcinolone acetonide in their study [16].

The present study is aimed at evaluating the therapeutic efficacy of subretinal BSS injections in conjunction with conventional vitrectomy for refractory DME resistant to more than one anti-VEGF agent, intravitreal corticosteroids, and to previous vitrectomy.

2. Materials and Methods

This study was a prospective, interventional noncomparative case series. The author adhered to the tenets of the Declaration of Helsinki. All patients were informed about the risks and benefits of the surgery, and written consent was obtained after thorough explanation of the procedure in clear simple words. The study was approved by the Institutional Review Board and the Ethics Committee at the Faculty of Medicine, Alexandria University.

Twenty-eight eyes of 28 patients with DME resistant to anti-VEGF and corticosteroid (Cst) therapy were included in this study. Some had already undergone pars plana vitrectomy for refractory DME. In all cases, vitrectomy was performed with subretinal injection of BSS between November 2015 and November 2017.

The inclusion criterion for eyes with refractory DME was a central macular thickness (CMT) of more than 300 μm despite undergoing anti-VEGF therapy (5-6 monthly injections of ranibizumab (IVR) or bevacizumab (IVB) with shifting to aflibercept (IVA) for additional three injections). Some cases received Cst injection as well, before attempting this surgical solution in the form of intravitreal triamcinolone acetonide (1 or 2 injections) three months apart. All cases were psuedophakic. Cases subjected to conventional vitrectomy with internal limiting membrane (ILM) peeling were also enrolled in the study.

They were analysed after subdivision into group 1, including cases in which vitrectomy was not attempted, and group 2, including cases with persistent edema despite a previous vitrectomy (performed at least 6 months before the intervention). The cases were also divided into two groups: group a with normal vitreomacular interface (VMI) (defined as the absence of either perifoveal vitreoretinal attachment within 2500 μm of the foveal center or hyperreflective inner retinal band), group b with vitreomacular abnormality (VMA) in the form of ERM (defined as a hyperreflective inner retinal band with or without associated retinal inner surface plication).

The major exclusion criteria were (1) the presence of apparent retinal pigment epithelium (RPE) atrophy at or near the macula; (2) the presence of proliferative diabetic fibrovascular membranes threatening or at the macula; (3) the presence of diabetic optic atrophy; and (4) the presence of neovascular glaucoma.

All patients underwent complete ophthalmologic examinations with special emphasis on best-corrected visual acuity (BCVA) using the 6 m Landolt C acuity chart (converted to decimal) and indirect and contact lens slit lamp biomicroscopy. Spectral domain or swept source OCT (Cirrus; Carl Zeiss Meditec Inc., Dublin, CA; Spectralis; Heidelberg Engineering GmbH, Heidelberg, Germany) was used to examine all eyes before surgery and at 1 month and at the final visit after surgery. Central retinal thickness was defined as the distance between the inner surface of the RPE and the inner surface of the neurosensory retina at the macula. All patients were followed up for at least 10 months.

2.1. Data Analysis. To evaluate the surgical outcomes, preoperative and postoperative CMT and BCVAs of both groups (1, 2) and (a, b) were compared using paired tests. Significance was considered starting at a cut-off p value of 0.05. All statistical analyses were performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL). Quantitative data are presented as mean ± standard deviation, while qualitative data are represented in number and percentage.

2.2. Surgical Technique. The surgery was performed using a 23-gauge, transconjunctival, microincision vitrectomy system. After core vitrectomy, posterior hyaloid detachment was attempted with the vitrectomy cutter in the suction mode. We then stained the ILM with dual stain (Membrane-Blue-Dual, DORC International), which contains a combination of 0.15% trypan blue, 0.025% Brilliant Blue G (BBG), and 4.00% polyethylene glycol (PEG). It was injected under air and left there for 30 seconds. Subsequently, the ILM peeling was attempted and peripheral vitrectomy was carried out as the peripheral residual vitreous was more evident after the dual stain application. We then injected 0.3–0.5 ml of BSS

into the subretinal space to detach the fovea, ensuring that the foveal detachment covered the entire area with DME. This injection of BSS was performed at the site where the ILM had been removed using a 38-gauge cannula (MedOne Surgical Inc., Sarasota, FL) with a pressure of 4 to 6 psi (viscous fluid control system, Alcon Laboratories, Fort Worth, TX) [17] (Video 1).

In cases with VMI abnormality, the EMM was peeled using an end-gripping 23-gauge forceps after staining with dual stain, which stains both the ILM and the ERM. Then, ILM peeling was attempted with the 23-gauge end-grasping forceps (Rumex International Co., USA). Subretinal injection of BSS was done as mentioned above (Video 2).

In eyes with persistent DME despite previous vitrectomy, staining was also done under air to ensure ILM removal above the entire area involved in the edema process and proper peripheral vitreous trimming before attempting subretinal BSS injection (Video 3).

2.3. Endpoints. The primary endpoint for this study was the change in CMT at the final visit (from 9–12 months after surgery). The secondary endpoints were change in BCVA at the final visit after surgery, recurrence of DME, and surgical complications. The state of the ellipsoid zone and the ELM (as shown by the preoperative OCT) was also compared to its appearance in the OCT taken during the final visit. Recurrence of DME was defined as an increase in CMT $\geq 10\%$ of the least thickness attained during the period of follow-up, with concomitant drop of at least one line of BCVA.

3. Results

3.1. Preoperative Characteristics. The study included 28 eyes of 28 patients with a mean age of 53.1 ± 7.2 years. All eyes had CME, with 13 eyes (46.4%) suffering from neurosensory detachment (NSD), while only 6 eyes (21.4%) had vitreomacular interface abnormality (VMA) in the form of a fine epimacular membrane. Thirteen eyes (46.4%) received IVB followed by 3 IVA injections before including them in this study, while 16 eyes (57.1%) received preoperative IVR followed by 3 IVA before rendering them refractory and including them in the study. CST was given in 12 eyes (42.9%) after failure of either protocol of anti-VEGF to decrease CMT.

As regards the preoperative OCT finding, preoperative ellipsoid zone was intact in 13 eyes (46.4%) and disrupted in the rest of the included eyes. The preoperative ELM was intact in 12 eyes (42.9%) preoperatively. In 7 eyes (25%), a vitrectomy with ILM peeling was carried out for refractory DME 6 months prior to their inclusion in this study.

3.2. Operative Complications. Intraoperative complications were identified in three eyes. An iatrogenic macular hole occurred in two eyes (7.1%) during subretinal BSS injection, but postoperatively, the hole was found to be closed with improvement of BCVA (Video 1). In another case, an iatrogenic break occurred in the nasal retina during injection of the dual stain. Endolaser was applied, and the patient was instructed to attain a prone position for two days.

3.3. Postoperative Findings. The cases had a mean follow-up period of 10.6 ± 1.1 months postoperatively. The mean preoperative CMT was $496.07 \pm 88.7\,\mu$m, while the postoperative mean CMT decreased to $335 \pm 67\,\mu$m, when measured 4 weeks postoperatively. The mean CMT further dropped with subsequent OCT measurements and reached a mean of $274.1 \pm 31.6\,\mu$m at the final follow-up visit for all included eyes ($p = 0.029$).

Six eyes (21.4%) suffered from recurrence of their edema defined as increase in CMT by more than 10% of the least thickness attained during the period of follow-up, with concomitant drop of at least one line of BCVA. Intravitreal triamcinolone (IVTA) (once in 2 eyes and twice in 4 eyes) was given to treat these recurrences. All these eyes showed improvement of CMT and BCVA after IVTA and regained the postintervention parameters (Figure 1).

In all operated 28 eyes, the preoperative mean $\pm$ SD BCVA in decimal form was 0.2 ± 0.11, while at the final follow-up visit, the mean $\pm$ SD BCVA improved to 0.45 ± 0.2 ($p = 0.000019$). No improvement occurred postoperatively in the ellipsoid zone integrity in all eyes even in those with complete resolution of edema. Despite this finding, BCVA did improve in eyes with edema resolution to different extents. As for the ELM, postoperative 16 eyes (57.1%) showed continuous ELM with resolution of edema.

3.4. Subgroup Analysis. Cases were divided into group 1 which included eyes where vitrectomy was not attempted as a solution for refractory DME (Figure 2) and group 2 which included eyes with a history of vitrectomy for more than 6 months (Figure 3). Table 1 shows the pre- or postoperative characteristics of the two groups.

Eyes included were also divided into group a (with normal vitreomacular interface) and group b (vitreoretinal abnormalities present in the form of ERM, Figures 3 and 4). Table 2 shows a comparison between groups a and b.

4. Discussion

Despite all the pharmacological and surgical interventions currently utilized for refractory DME, the results for many cases are disappointing. This led to the introduction of the planned foveal separation with submacular BSS injection with favorable results [15]. In addition to its success in cases in which all other treatment protocols failed, a rapid edema resolution was noticed. The technique was associated with intact ELM and ellipsoid zone on OCT and better visual outcomes which was clearly depicted in previous studies tackling this point [13, 14, 18–20]. Yet, this technique had not been previously attempted in vitrectomized eyes and in those with ERM.

The refractory edema responded better with this technique than with conventional vitrectomy with or without ILM peeling. This was shown by Ulrich et al., who found that there was no significant change in CMT at 1 and 3 months after conventional vitrectomy, ($p = 0.91$, 0.29) or in visual acuity ($p = 0.69$, 0.21). However, it was not until 6 months postoperatively that the CMT had significantly decreased ($p = 0.03$) and the visual acuity showed

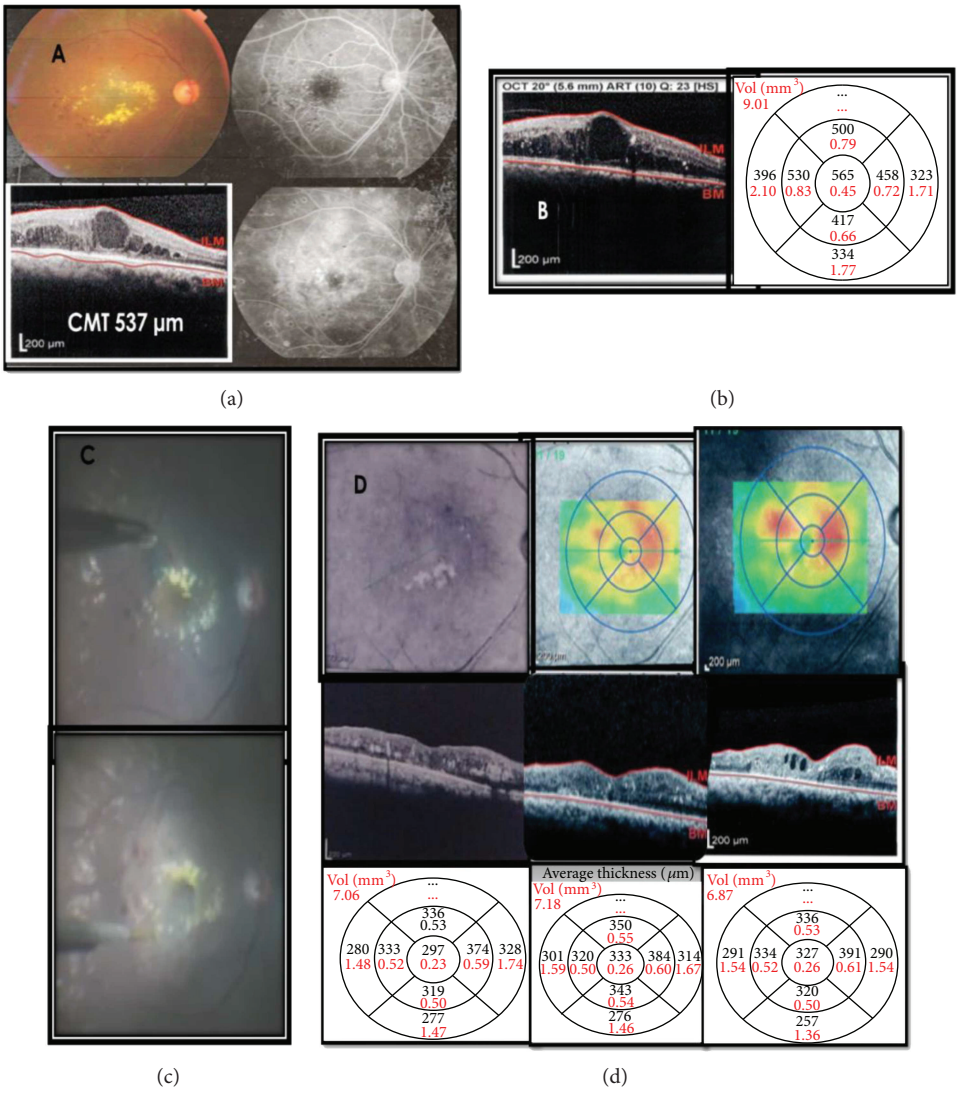


Figure 1: (a) Preoperative color fundus photo and FA showing diffuse DME with foveal hard exudate accumulation, CMT by OCT measuring 537 microns after 9 IVB injections over 1 year, BCVA measuring 0.1. (b) OCT after 3 IV triamcinolone (TA) injections 3 months apart with CMT measuring 565 microns and no improvement in BCVA. (c) Upper photo showing ILM peeling after dual stain application, while lower phot showing submacular BSS injection. (d) Red free showing significant decrease in amount of hard exudates 1 month postoperation, with drop of CMT to 297 microns and BCVA improvement to 0.3. Middle OCT with the thickness map showing recurrence of DME measuring 333 microns 6 months postoperation. The right-hand side OCT image and thickness map after 2 IVTA injections 2 months apart with slight CMT improvement of 327 microns while regaining a BCVA of 0.3 which was measured 10 months postoperation.

improvement ($p = 0.0$) [19]. Similarly, the Diabetic Retinopathy Clinical Research Network reported that 3 months after vitrectomy, the decrement in CMT was only 160 μm [7]. Likewise, Yamamoto et al. observed that although the CMT decreased by 140 μm 1 week after surgery, it took 4 months for the CMT to drop below 300 μm [9].

The current study demonstrated a more rapid and significant decrease in CMT: by 163.9 ± 32.6 μm after 4 weeks and 227.01 ± 80.01 μm at the final visit (10.6 ± 1.2 months) in group a and by 147.97 ± 16.2 μm after 4 weeks and 203.17 ± 70.4 μm at the final visit (10.5 ± 0.5 months) in group b, but this difference was not statistically significant ($p = 0.645$). Likewise, BCVA improved in group a from a mean of 0.2 ± 0.11 preoperatively to a mean of 0.44 ± 0.2 postoperatively and from a mean of 0.217 ± 0.11 preoperatively to 0.5 ± 0.22 postoperatively in group b. These values were again not statistically significant. These results indicate that the planned foveal detachment technique works like an adjunctive step to conventional vitrectomy to speed up the resolution of DME and improve BCVA, regardless of the vitreomacular interface state before the surgery.

The rapid resolution of macular edema by the planned foveal detachment technique was noticed to be more in surgically naïve DME patients (group1) measuring 239 μm at the final follow-up visit than in group 2 eyes, subjected previously to both anti-VEGF and conventional vitrectomy, reaching 170.8 μm at the final follow-up visit. This difference in outcome was statistically significant ($p = 0.019$).

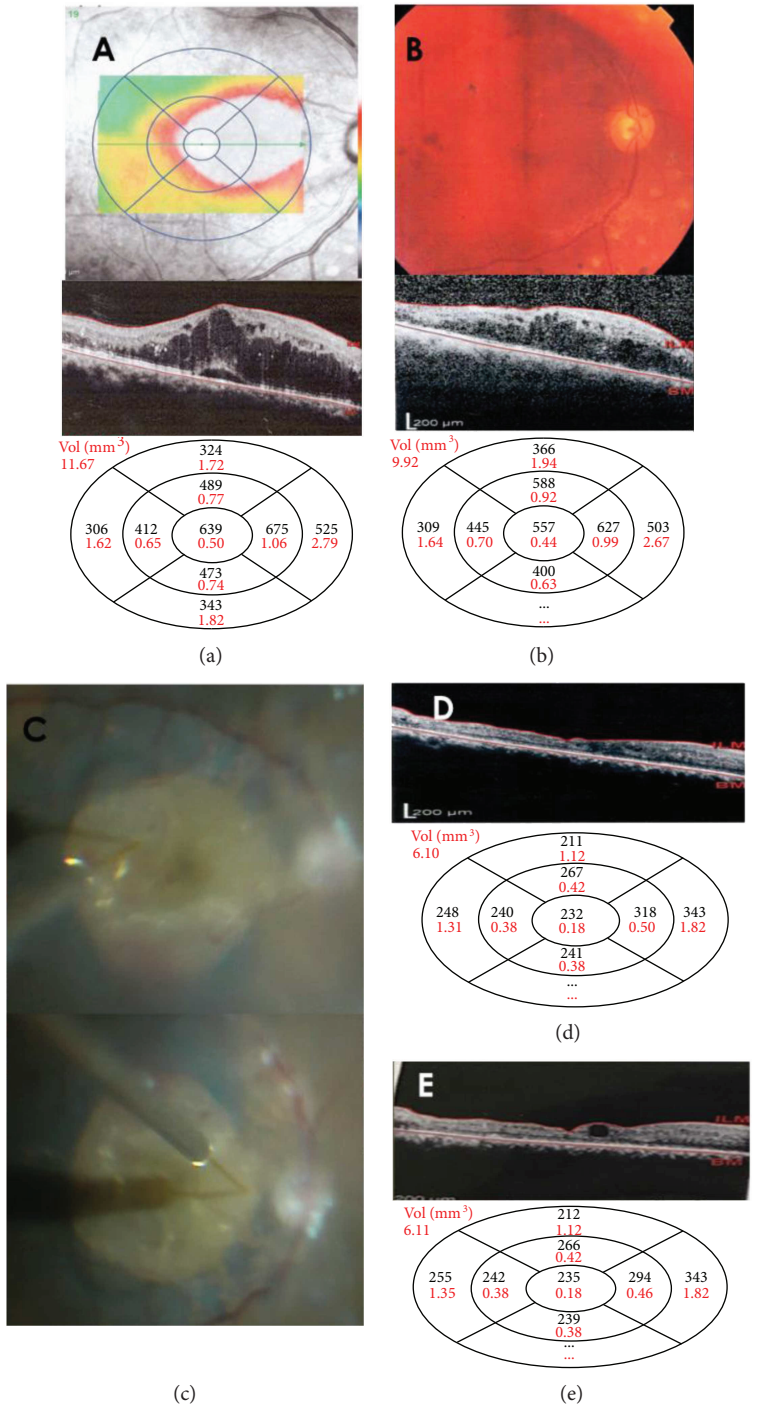


Figure 2: (a) Right eye: preoperative red free color-coded map showing marked DME with cystoid and neurosensory detachment shown in the OCT image, disruption of both ellipsoid zone, and ELM, with CMT measuring 639 microns after 8 IVR injections and 3 IVA injections over 1 year with BCVA equals 0.06. (b) Color fundus photo and OCT image of the same eye after two IVTA injections with CMT improving to 557 microns, but BCVA remained at 0.06. (c) Subretinal BSS injection after ILM peeling done at 2 different sites to cover the entire area of edema. (d) OCT image showing complete resolution of edema 4 weeks postoperatively with a CMT of 232 microns and BCVA of 0.16. The ellipsoid zone and ELM integrity were not regained. (e) CMT measured 10.2 months later equals 235 microns with stable BCVA.

As regards the visual acuity, the preoperative BCVA in group 1 (surgically naïve eyes) was 0.16 ± 0.07, which improved to a mean of 0.34 ± 0.09, while in group 2 (eyes with previous vitrectomy), the preoperative BCVA was 0.37 ± 0.14, which improved to a mean of 0.7 ± 0.16 postoperatively. This was not statistically significant ($p = 0.185$). So, although there was a significant difference in the mean CMT between the two groups (1 and 2), the mean BCVA postoperatively did not differ significantly. This might be explained by the fact that the chronicity of the edema in

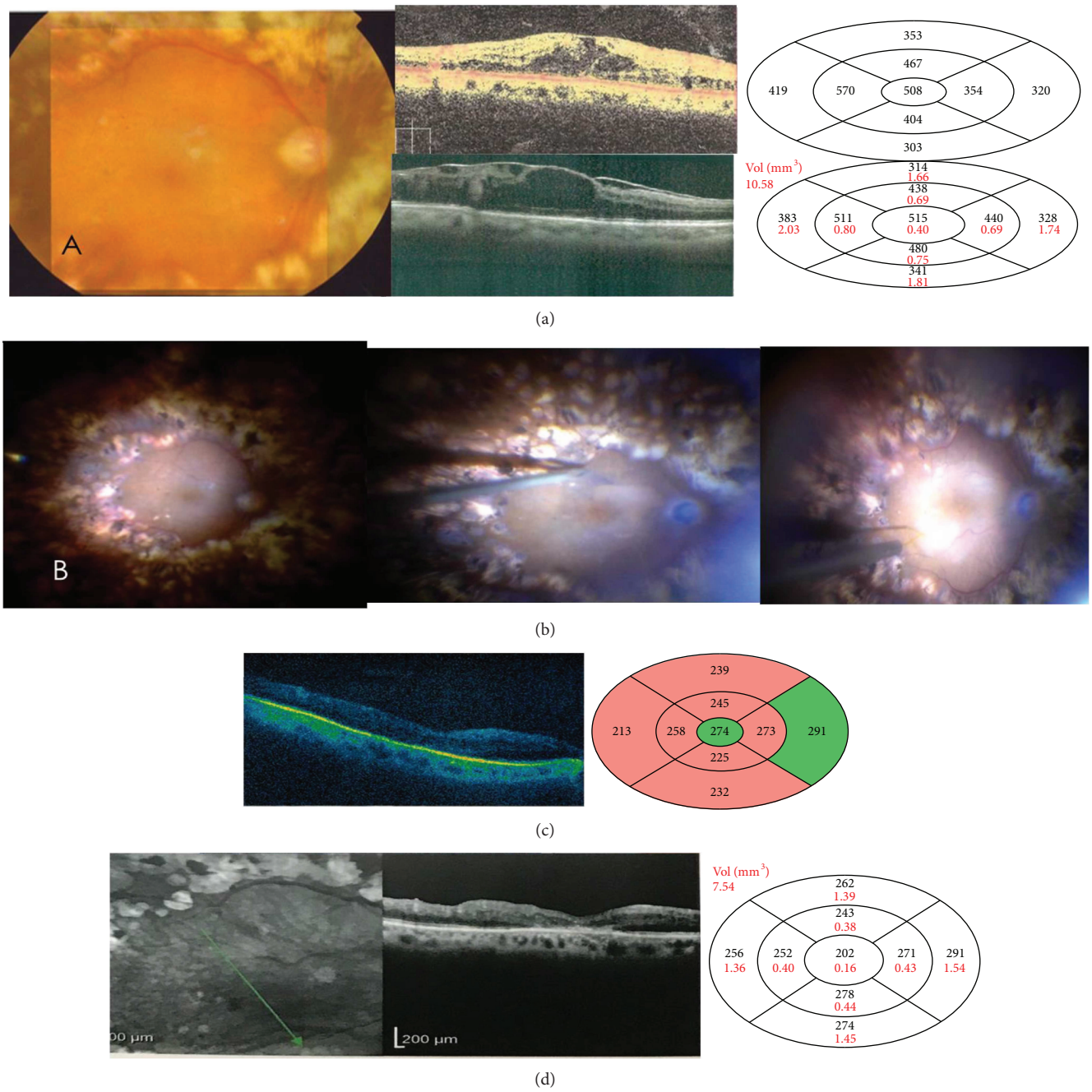


Figure 3: (a) Color fundus photo of a 59-year-old female who had vitrectomy done for refractory DME after failure of anti-VEGF (10 IVB and 3 IVA) to improve the edema. Upper OCT image and map showing CMT of 508 microns a year after the vitrectomy with BCVA of 0.05, totally disrupted ellipsoid zone and ELM. Lower OCT image and thickness map after 3 IVTA injections 3 months apart as a trial to improve the edema, CMT measuring 515 microns without VA gain and appearance of an ERM. (b) During surgery, ILM peeling was reattempted, and submacular BSS was injected to cover the whole area of the edema. (c) OCT of the macula 1 month postoperatively shows resolution of the edema with CMT 274 microns and BCVA of 0.1. (d) Red free photo 9.5 months postop. with thickness dropped further to 202 microns and BCVA still 0.1, probably due to the marked ELM and ellipsoid zone disruption.

both groups was a limiting factor against marked BCVA improvement despite the greater improvement in CMT. This was obvious in group 1 where similar improvement in postoperative BCVA occurred despite a marked drop of CMT in relation to group 2.

The superiority of planned foveal detachment may be explained by multiple factors according to Morizane et al. These include facilitation of egress of edema fluid from the retina to the choroid by reducing both the oncotic pressure and viscosity of the subretinal fluid as well as the wash out of inflammatory cytokines and migratory cells above the RPE. Both mechanisms might be responsible for activation of the RPE to pump fluid from the retina to the choroid. Since these mechanisms could be effective within hours or days of surgery,

Table 1: Pre- and postoperative characteristics of groups 1 and 2.

Variable studied	Group 1	Group 2	p value
Number of eyes in each group	21	7	
Age mean ± SD (years)	53.38 ± 8.2	52.7 ± 3.4	
OCT findings			
Presence of neurosensory detachment preoperatively	9 (42.9%)	4 (57.1%)	0.51
Presence of VMA preoperatively	3 (14.3%)	3 (42.9%)	0.11
Intact ellipsoid zone	10 (47.6%)	3 (42.9%)	0.827
Preop. continuous ELM	9 (42.9%)	3 (42.9%)	1.0
Postop. continuous ELM	13 (69.9%)	3 (42.9%)	0.3
Preoperative CMT mean ± SD (μm)	521.3 ± 83.6	420.2 ± 56.3	
Postoperative CMT (final visit) mean ± SD (μm)	282.3 ± 20.8	249.4 ± 45.7	0.019*
Preoperative injection history			
Bevacizumab + aflibercept	10 (47.6%)	3 (42.9%)	0.11
Ranibizumab + aflibercept	12 (57.1%)	4 (57.1%)	1.0
CST after anti-VEGF failure	8 (38.1%)	4 (57.1%)	
BCVA (decimal form)			
Preoperative	0.16 ± 0.07	0.34 ± 0.09	
Postoperative (final visit)	0.37 ± 0.14	0.7 ± 0.16	0.185*
Recurrence of edema within FU period	6 (28.6%)	0 (0.0%)	0.1
Follow-up period in months	10.57 ± 1.1	10.86 ± 1.2	

*Mann–Whitney test.

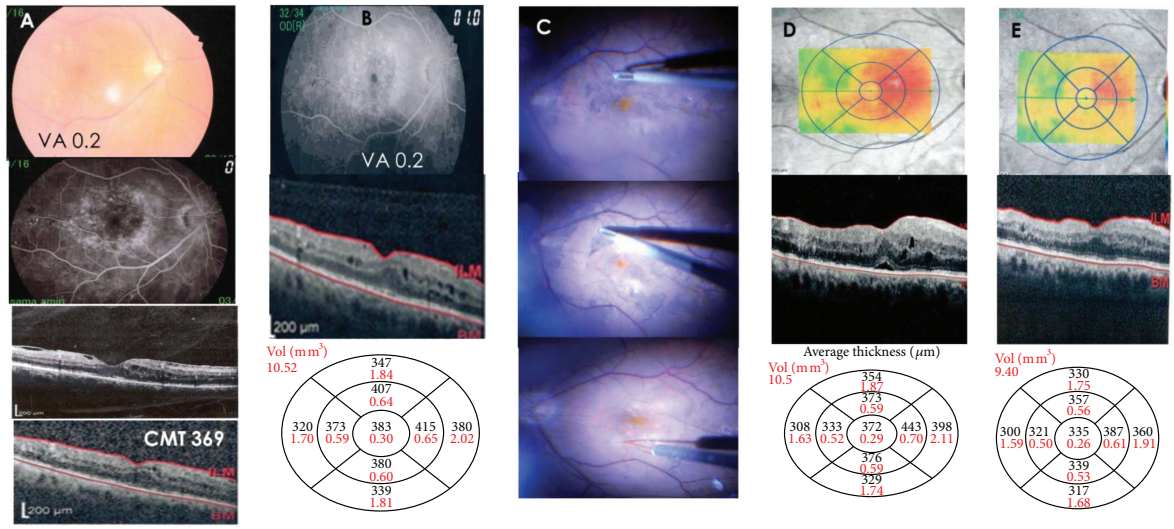
Table 2: Characteristics of group a (normal vitreomacular interface) and group b (vitreoretinal abnormalities present).

Variable studied	Group a	Group b	Significance (2-tailed)
Number of eyes in each group	22	6	
Age	52.82 ± 7.6	54.5 ± 6.3	
Previous vitrectomy attempted	4 (18.2%)	3 (50.0%)	0.288
Follow-up in months	10.68 ± 1.2	10.5 ± 0.5	
OCT characteristics of the 2 groups			
Preoperative mean ± SD CMT (μm)	497.6 ± 93.1	490.3 ± 77.3	
CMT at 4 weeks	333.7 ± 69.7	342.33 ± 61.1	
Final CMT	270.5 ± 33.9	287.1 ± 16.6	
CMT improvement	227.01 ± 80.01	203.17 ± 70.4	0.645*
Intact ELM at final visit	14 (63.6%)	2 (33.3%)	0.354
BCVA in decimal form			
Preoperative	0.2 ± 0.11	0.217 ± 0.11	
Final	0.44 ± 0.2	0.5 ± 0.22	
Lines of improvement	3.82 ± 29	3.67 ± 1.21	0.883*
Recurrence of macular edema	6 (27.3%)	0	0.289
Complications			
Macular hole	1 (4.5%)	1 (4.5%)	0.529
Iatrogenic break	1 (16.7%)	0 (0.0%)	0.435

*Mann–Whitney.

they were consistent with their observations of rapid complete resolution of the macular edema after surgery [15].

In the present study, it is also notable that the resolution of DME continued for at least 10 months without additional treatment in most cases (22 eyes, 78.6%). This long-term effect may be explained by the fact that marked and rapid improvement in the retinal environment, due to drainage of the edema fluid, breaks the vicious cycle of ischemia-vascular hyperpermeability-chronic inflammation-ischemia seen in diabetic patients [15].



(a) (b) (c) (d) (e)

Figure 4: (a) Color fundus photo and late FA image of a male 53 years of age with type 2 DM, suffering from refractory DME with VMA with a CMT of 369 microns after 8 IVR injections over the past 9 months. BCVA recorded was 0.2. (b) Diffuse DME shown in a late FA image with CMT of 383 after shifting to IVA for three consecutive injections. (c) Upper snap shot during removal of the fine ERM stained with the dual stain, middle image showing ILM peeling, while the lower photo was taken during submacular BSS injection. (d) Red free with color-coded map showing slight CMT improvement 4 weeks postoperatively reaching 372 microns. (e) Eight months postoperation with edema reaching 335 without additional treatment and BCVA improved to 0.8.

During the surgical procedure for the planned foveal detachment technique, special attention is needed to avoid an iatrogenic macular hole or injuries to Bruch's membrane during the subretinal injection of BSS. Therefore, Morizane et al. used a viscous fluid-control system (Alcon Laboratories, Fort Worth, TX, USA) with a low injection pressure to regulate the speed of subretinal injection [15].

In the present study, a similar maneuver was used for subretinal fluid injection. Still, 2 cases (7.1%) suffered iatrogenic holes during injection. However, the postoperative follow-up revealed closure of the macular holes with improvement of the final visual acuity in these cases. Even without submacular saline injection, the risk of macular hole induction exists, as Grigorian et al. reported an incidence of 2% with conventional vitrectomy for DME [21].

Most of the cases included in the current study have had DME for more than a year, with significant ellipsoid zone (EZ)—previously called the photoreceptor inner segment/outer segment (IS/OS) junction—disruption in 15 eyes (53.6%). In these cases, ellipsoid zone disruption neither improved nor worsened postoperatively. Despite this, the CMT, BCVA and, to a certain extent, the ELM continuity improved after resolution of edema postoperatively. A similar conclusion was drawn by Chhablani et al., where the strongest clue for vision improvement was preoperative damage to the ELM ($p = 0.0277$) compared to the IS/OS junction ($p = 0.03$) [22].

In conclusion, vitrectomy with planned foveal detachment technique appears to be a promising solution for DME cases that is resistant to all other forms of treatment (repeated anti-VEGF, Cst injections, and even conventional vitrectomy with ILM peeling) with rapid and efficient edema resolution in those resistant eyes. CMT was better in eyes where conventional vitrectomy was not attempted. Moreover, cases with VMA resistant to pharmacotherapy was shown to respond well to this technique.

The current study is limited by its uncontrolled design and small sample size. Further randomized controlled clinical studies involving a larger number of patients with longer duration of follow-up are needed to define the exact role of this procedure in the management of DME.

Conflicts of Interest

The author declares that there is no conflict of interest regarding the publication of this paper.

Supplementary Materials

Video 1: edited video showing the ILM peeling in a surgically naïve case with a refractory DME in spite of 9 IVB injections during the course of 1 year and 3 IV triamcinolone (TA) injections 3 months apart, BCVA measuring 0.1. Secondary iatrogenic macular hole occurred during submacular BSS injection. Fluid-air exchange at the end of the surgery. Video 2: edited video showing a case with fine EMM and refractory DME in spite of repeated ranibizumab injections and 3 aflibercept injections along the course of 8 months, the EMM that was peeled using an end-gripping 23-gauge forceps after staining with dual stain, subretinal injection of BSS was attempted as mentioned above. Fluid air exchange was then done. Video 3: edited movie for an eye with persistent DME despite previous vitrectomy, staining was also done under air to ensure ILM removal above the

entire area involved in the edema process and proper peripheral vitreous trimming before attempting subretinal BSS injection was done. Air was left as a tamponade at the conclusion of surgery. *(Supplementary Material)*

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Research Article

Evaluation of Navigated Laser Photocoagulation (Navilas 577+) for the Treatment of Refractory Diabetic Macular Edema

Fusae Kato, Miho Nozaki, Aki Kato, Norio Hasegawa, Hiroshi Morita, Munenori Yoshida, and Yuichiro Ogura

Department of Ophthalmology and Visual Science, Nagoya City University Graduate School of Medical Sciences, 1-Kawasumi, Mizuho-ku, Nagoya 467-8601, Japan

Correspondence should be addressed to Miho Nozaki; miho.nozaki@gmail.com

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Purpose. To evaluate navigated laser photocoagulation for the treatment of refractory diabetic macular edema (DME). *Methods*. Retrospective study of 25 eyes (21 patients) treated with Navilas 577+ focal laser system. Best-corrected visual acuity (BCVA) and spectral-domain optical coherence tomography (OCT) parameters were measured at baseline, 1, 3, and 6 months, and final visit. *Results*. The mean follow-up period was 12.8 ± 2.4 (7–16 months). All subjects had history of previous treatment which was injection of triamcinolone acetonide or antivascular endothelial growth factor (VEGF) agents. The navigated laser photocoagulation was delivered to the microaneurysms on indocyanine green angiography (ICGA) in 21 of 25 eyes (84%), fluorescein angiography (FA) guided in 3 eyes, and OCT angiography guided in 1 eye. After initial navigated laser treatment, 16 of 25 eyes (64%) were needed additional navigated laser photocoagulation, injection of triamcinolone acetonide, and/or injection of VEGF agents. Although median BCVA remained stable, the central retinal thickness and macular volume were significantly decreased over 6 months ($p < 0.05$). All patients were treated without complications. *Conclusions*. Focal photocoagulation using Navilas 577+ showed to be effective in treating DME with improvement in macular edema on OCT over 6 months. Navilas 577+ was beneficial to perform navigated laser photocoagulation based on three modalities (ICGA, FA, and OCT angiography).

1. Introduction

Diabetic macular edema (DME) occurs due to a malfunction of the blood-retinal barrier and death of endothelial cells leading to leakage of fluid and subsequent photoreceptor dysfunction [1, 2]. Focal laser treatment leads to the occlusion of these leaking microaneurysms (MAs), pathologic vessels, or subretinal sites of leakage [3]. As the Early Treatment Diabetic Retinopathy Study (ETDRS) research group showed, focal laser therapy can reduce moderate to severe vision loss, but the major effects were not seen till after 3 years of follow-up [4]. On the other hand, the advent of antivascular endothelial growth factor (VEGF) agents showed rapid and prominent effects on vision improvement in numerous multicenter trials [5–9]. Anti-VEGF agents have become the first-line treatment for DME. However, this treatment requires repeated intravitreous injections for an indefinite period, and safety concerns regarding to long-term systemic suppression of VEGF, which is a serious risk of cerebrovascular accidents especially in elderly patients, are emerging [10]. Recent meta-analysis has shown type 2 diabetic patients with DME or proliferative diabetic retinopathy (PDR) were associated with a twofold higher risk of fatal cardiovascular accidents compared with those without DME or PDR [11]. Therefore, a new optical treatment modality should be developed to improve the cost-effectiveness, safety, and visual outcomes. Liegl et al. reported the efficacy of a standardized combination therapy regimen (three

ranibizumab injections followed by navigated focal laser) [12]. In their analysis, combination therapy regimen was significantly lower compared to ranibizumab monotherapy in terms of retreatment rate and number of injections among 12 months.

The navigated laser photocoagulator, also known as the Navilas laser system (OD-OS GmbH, Teltow, Germany), is computer-based system combined with wide-angle imaging camera. The Navilas has eye-tracking laser delivery system and allows more accurate for focal laser photocoagulation than conventional focal laser therapy for DME [13, 14]. The Navilas laser photocoagulation is performed based on preplanned treatment locations with the real-time fundus image. Navilas 577+ laser system is the new model of navigated laser system and has been approved in Japan in 2016. The preplanned treatment can be made based on color image, fluorescein angiography (FA), indocyanine green angiography (ICGA), optical coherence tomography (OCT), and/or OCT-angiography.

The aim of this study is to evaluate navigation laser photocoagulation (Navilas 577+ laser system) for the treatment of refractory DME patients.

2. Materials and Methods

This study was a retrospective, noncomparative case series performed at the eye center of Nagoya City University Graduate School of Medical Sciences. Institutional Review Board (IRB) approval (#60-17-0108) was obtained for the study protocol and procedures. The study adhered to the tenets of the Declaration of Helsinki.

Twenty-five eyes of 21 patients (14 men and 7women) with DME were included in this study between April 2016 and October 2016. The mean age was 68.3 ± 9.2 years (range 42–80 years). The mean follow-up period was 12.8 ± 2.4 (7–16 months). Before navigated laser treatment, 13 of 25 eyes (52%) had received sub-Tenon's injections of triamcinolone acetonide (TA) (Kenacort; Bristol-Myeres Squibb, Tokyo, Japan) and 12 or 25 eyes (48%) had received ranibizumab and/or aflibercept injections. Four eyes had received subthreshold laser using PASCAL Streamline (Topcon Medical Laser Systems, Santa Clara, CA, USA), and three eyes had received manual focal laser. One eye had received vitrectomy. There were some that overlapped in treatment history (Table 1).

All participants underwent a complete ophthalmologic examination, including the best-corrected visual acuity (BCVA), intraocular pressure, slit-lamp and indirect ophthalmoscopy, and OCT. The BCVA was measured with a Japanese standard decimal visual acuity chart, and decimal BCVA was calculated using the logarithm of the minimum angle of resolution (LogMAR) scale. Spectral-domain OCT (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA) was performed to evaluate morphological retinal changes, central retinal thickness (CRT), and macular volume (MV). FA and ICGA using the Heidelberg Spectralis HRA II (Heidelberg Engineering, Heidelberg, Germany) were performed to detect the leakage of MAs. DME type was classified as focal or diffuse based on the features below. The characteristics of focal macular edema are (1) location outside the foveal center with or without center involvement; (2) asymmetric increases in retinal thickness on OCT scan; and (3) accumulation of pin-point leakage in early phase. The characteristics of diffuse macular edema are (1) increased retinal thickness with center involvement on the OCT macular thickness map; (2) symmetrically increased retinal thickness on B-scan OCT; and (3) fluorescein leakage starting from early phase and continuously increasing to late phase [2]. Fifteen eyes (60%) were classified as focal and 10 eyes (40%) were classified as diffuse edema.

Table 1: Baseline characteristics of patients.

Characteristic	Value
Number of eyes/patients	25 eyes/21 patients
Sex, *n* (%)	
Male	14 (64%)
Female	7 (36%)
Age (years)	
Range	42–80
Mean ± SD	68.3 ± 9.2
HbA1C (%)	
Mean ± SD	7.1 ± 1.2
Previous treatments, *n*	
STTA	13*
Anti-VEGF (ranibizumab, aflibercept)	12*
Subthreshold laser	4*
Conventional focal laser	3*
Vitrectomy	1*

*Including the overlap; VEGF: vascular endothelial growth factor; STTA: sub-Tenon's injections of triamcinolone acetonide.

A yellow wavelength (577 nm) photocoagulation was planned to target the leaking MAs and performed by the Navilas laser system. Briefly, treatment plan was made by physicians on a static image from FA, ICGA, and/or OCTA. The image which registered and overlaid onto the live retinal image in real time was on placing laser spot marks. After photocoagulation, a color image of the fundus was acquired to confirm that all laser applications accurately hit the preplanned points. In follow-up examinations, the patients received additional photocoagulation or medications if there were persistent of MAs or there were no findings of reduction in CRT.

Statistical analyses were performed with SPSS statistics 22 (IBM Corp., Armonk, NY, USA). In evaluating BCVA, CRT, and MV, changes (1, 3, 6 months and final visit) from baseline were analyzed using one-way repeated measures ANOVA and Bonferroni correction as post hoc test. A p value of <0.05 was considered statistically significant.

3. Results

The initial navigated laser photocoagulation was delivered to the MAs on ICGA in 21 of 25 eyes (84%). Three eyes underwent FA-guided photocoagulation. One eye had the allergy of dye injection and had undergone navigated

photocoagulation on OCT angiography (Avanti OCT; Optovue, Fremont, CA, USA). The mean laser parameters were a spot size of 50–100 μm, duration between 20–100 milliseconds (ms), and power between 50–100 milliwatts (mW). Each patient received an average of 22 ± 17 burns for successful treatment. The initial laser application was performed without a contact lens in 12 of 25 eyes (48%).

After initial Navilas laser treatment, 9 of 25 eyes (36%) did not need any retreatments due to resolution of DME, although 4 eyes received sub-Tenon's injections of TA simultaneously. In other subjects, macular edema remained. Two eyes received intravitreal aflibercept (IVA) prior to navigated laser treatment within 4 weeks and 9 eyes were received IVA after navigated laser treatment. The average number of IVA is 1.55 ± 1.00 between 6 months. Some eyes received sub-Tenon' injections of TA and/or intravitreous injection of TA (MaQaid; Wakamoto Pharmaceutical Co., Ltd., Tokyo, Japan). Eleven eyes (44%) carried out additional Navilas laser photocoagulation. Three eyes were performed subthreshold laser, and 2 eyes were performed focal laser treatment by the slit-lamp delivery laser system (PASCAL Streamline) (Table 2).

Changes of mean visual acuity and parameters of OCT were showed in Figure 1. Mean logMAR BCVA, CRT, and MV at baseline were 0.21 ± 0.32, 417.7 ± 108.3 μm, and 12.3 ± 1.9 mm^3, respectively. Mean CRT at 6 months and the final visit decreased significantly compared with baseline (month 6; 346.4 ± 110.4 μm, the final visit; 322.3 ± 78.6 μm, $p < 0.05$). Mean MV at 6 months and the final visit also decreased significantly compared with baseline (month 6; 11.5 ± 1.8 mm^3, final visit; 11.3 ± 1.3 mm^3, $p < 0.01$). There were no remarkable changes in mean LogMAR BCVA after the navigated laser treatment (month 6; 0.25 ± 0.34, final visit; 0.23 ± 0.33). Eight eyes (89%) of nonretreated group were focal DME, whereas seven eyes (44%) of retreated group were focal edema. The difference in the morphology of DME between the nonretreated and retreated groups was significant ($p < 0.05$, fisher's exact test). There were no complications related to laser treatment.

3.1. Representative Cases of ICGA-Guided Navilas 577+ Laser Photocoagulation. A 77-year-old man presented with vision deterioration of the right eye due to DME. OCT macular map image revealed fovea-involving macular edema, and leaking MAs were detected on FA and ICGA corresponding with the OCT thickness map findings. Although combined therapy with sub-Tenon's capsular injection of TA and ICGA-guided manual focal laser photocoagulation using PASCAL had been applied in March 2016, the macular edema remained a month later. The navigated laser photocoagulation was planned and performed based on ICGA in April 2016. There was resolution of DME in 3 months after the navigated laser treatment (Figures 2(a)–2(e)).

A 42-year-old female consulted to our hospital with a complaint of vision deterioration in the right eye, which was affected with DME developed after panretinal photocoagulation. The eye had the history of steroid-induced glaucoma. ICGA-guided Navilas laser photocoagulation was planned and underwent in April 2016. One month after the navigated laser photocoagulation, OCT findings on macular map and cross-sectional images became thinner and decimal visual acuity was remarkably improved from 0.5 to 0.8 (Figures 3(a)–3(e)).

Table 2: The details of additional treatment after initial navigated laser photocoagulation.

No retreatment, *n* (%)	9 (36%)
Single navigated laser	5 (20%)
Navigated laser + STTA	4 (16%)
Additional treatment	16 (64%)
IVA	11*
STTA	6*
IVTA	5*
Navigated laser	11*
Subthreshold laser	3*
Manual focal laser	2*

*Including the overlap; STTA: sub-Tenon's injections of triamcinolone acetonide; IVA: intravitreal aflibercept; IVTA: intravitreal triamcinolone acetonide.

4. Discussion

This retrospective case series of eyes with DME treated by Navilas 577+ laser system demonstrated reduction in CRT and MV at 6 months and final visit but no significant difference in logMAR BCVA. Moreover, other recent studies related to combination therapy of navigated laser and anti-VEGF agent have been published [12, 15, 16]. Their results indicate combination therapy is effective for visual gain and retinal stabilization, which can reduce number of injections. In our study, 11 eyes received injection of aflibercept following initial navigated laser, and their number of injection for 6 months were 1.55 ± 1.0, which was fewer than patients in major clinical trials [17]. As references, DME patients (23 eyes) treated anti-VEGF monotherapy in our institution received 2.52 ± 1.0 injections for the same duration of time. We considered there were two reasons why significant visual gain was not found in our study. One reason was many subjects had received several treatment histories before navigated focal laser was applied. The other was baseline BCVA in the current study was better than in those previous studies.

A randomized trial with navigated laser therapy (TREX-DME) for DME did not detect therapeutic benefits for navigated laser photocoagulation in visual gain and the CRT improved. The number of injections was not also significantly reduced at one year in combination therapy with anti-VEGF and navigated laser photocoagulation [18]. Although there was no significant difference in the mean maximal treatment interval with or without navigated laser photocoagulation, 38% of eyes with navigated laser photocoagulation were able to be maximally extended to 12 weeks, the benefit of adding navigated laser photocoagulation might be obvious with longer-term follow-up [18].

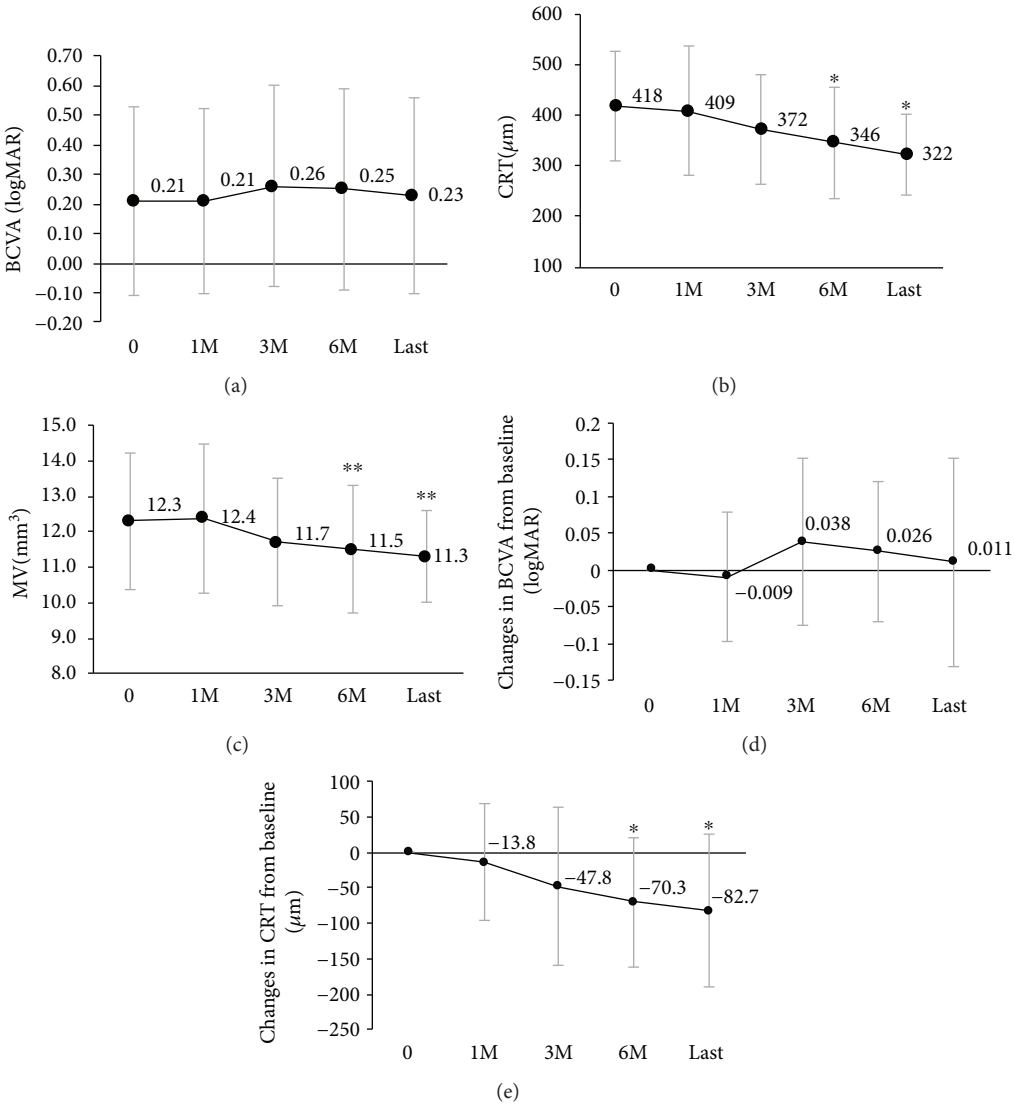
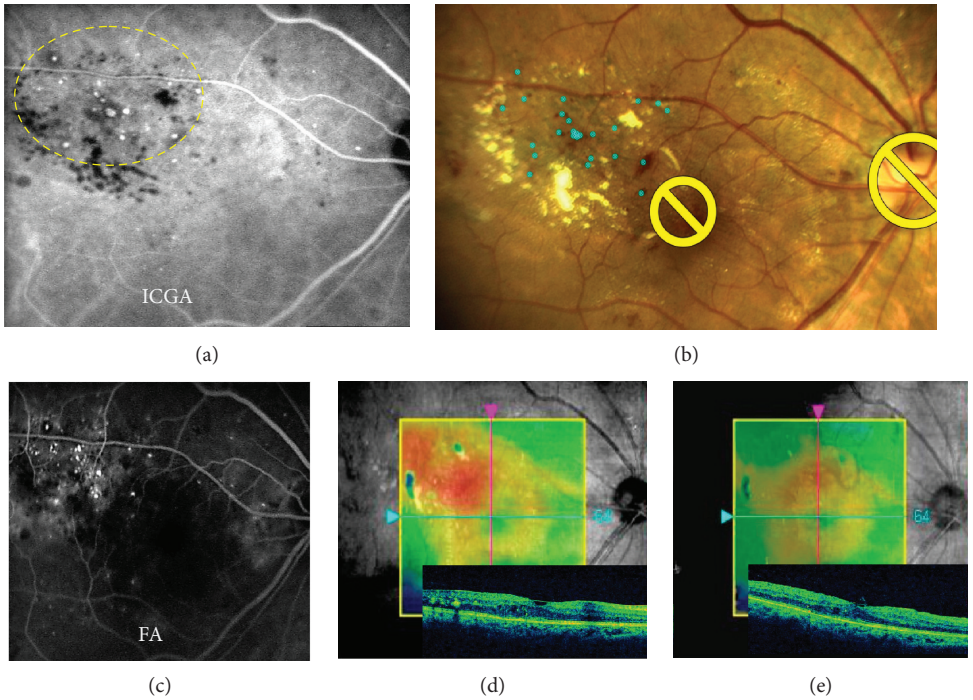


Figure 1: Comparison of pretreatment and posttreatment of the BCVA (a, d), CRT (b, e), and MV (c). The mean VA (± standard deviation) was unchanged from baseline to final visit; CRT and MV improved significantly ($^{*}p < 0.05$, $^{**}p < 0.05$). The comparison with baseline was evaluated by means of Bonferroni adjustment.

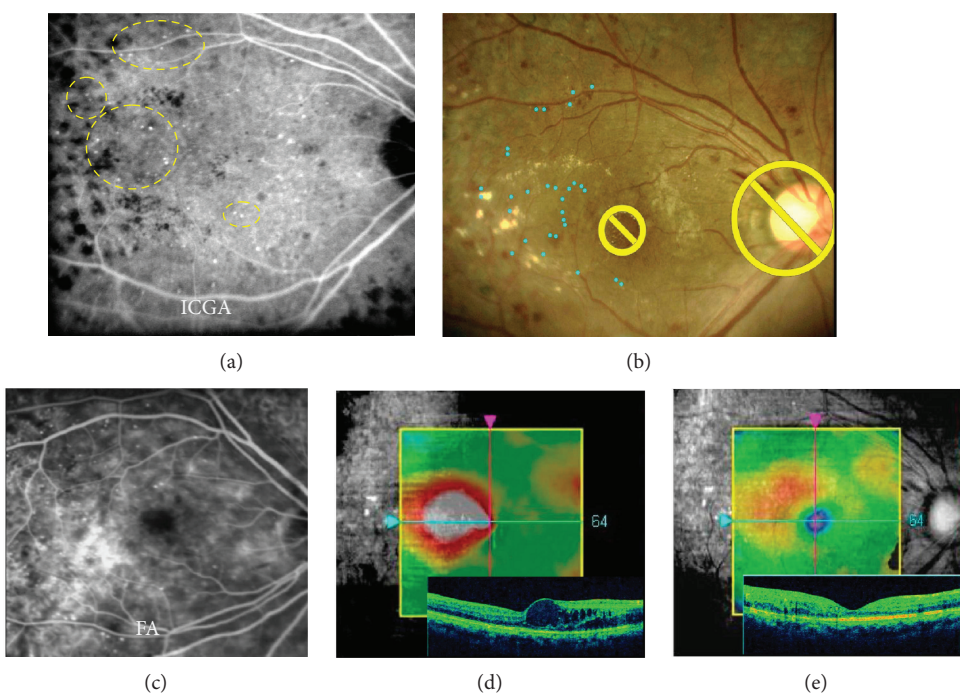
Predominantly, focal leakage from MAs showed less responsive to anti-VEGF therapy [19]. In our study, especially in cases where leaking MAs are mainly localized outside of the perifoveal capillary network, navigated laser therapy was effective. Other studies demonstrated combined conventional focal laser treatment could reduce the number of anti-VEGF injections for focal DME [7, 20]. To detect efficacy of focal laser therapy, it might be important individualized treatment be classified with different leakage subtype.

To mention with distinctive features in our current study, ICGA-guide navigated laser was performed to most of study eyes (84%). Indocyanine green dye is 98% bound to lipoproteins in the blood. Therefore, the dye hardly leaks, ICGA defines the detailed retinal vascular abnormalities better than FA [21–24]. Previously, we have reported that middle- to late-phase ICGA images show responsible MAs adjacent retinal edema, resulting in more precise and less number of focal laser photocoagulation spots [25, 26], and other groups also reported the clinical efficacy of ICGA-guided laser [27, 28]. However, it is difficult to identify the location of MAs on ICGA, due to lack of information of foveal avascular zone. So, the navigated laser system overlaid fundus image is suitable for treatment with ICGA-guided laser photocoagulation. The navigated photocoagulation seems to demonstrate a higher laser spot application accuracy in focal laser therapy of DME than conventional laser technique [13, 14]. However, in our study, 44% of eyes were required additional navigated laser photocoagulation. The result may mean that it takes time to become skilled in performing laser photocoagulation with navigation system. Navilas laser system enables physician to coagulate MA under observing the fundus directly. Especially conventional laser photocoagulation for MA, the aiming beam has been focused on forward to the retinal pigment epithelium (RPE). With Navilas, the location in the X-Y directions is accurate, but the focus in the z-axis is impossible to adjust. Boiko and Maltsev reported the larger



(a) (b) (c) (d) (e)

Figure 2: Representative case of ICGA-guided Navilas 577+ laser photocoagulation. A 77-year-old man underwent ICGA-guided navigated laser photocoagulation to treat DME which remained after focal laser using PASCAL (a–d). Image of treatment plan (blue dots) (b) was based on ICGA (a). After the navigated laser treatment, the macular edema was decreased in 3 months with no recurrences (e). The decimal visual acuity remained 0.9.



(a) (b) (c) (d) (e)

Figure 3: Representative case of ICGA-guided Navilas 577+ laser photocoagulation. A 42-year-old female underwent ICGA-guided navigated laser therapy (a–e). Some MAs were detected on late-phase ICGA indicated by yellow dashed line (a). Early-phase FA showed diffuse leakage from numerous MAs (c). Image of treatment plan (blue dots) (b) was based on ICGA (a). One month after the navigated laser photocoagulation, OCT findings on macular map and cross-sectional images became thinner and decimal visual acuity was remarkably improved from 0.5 to 0.8 (e).

diameter of laser burns and the more laser power needed following navigated focal laser in edematous retina compared with dry retina [29]. Therefore, it is recommended that navigated laser photocoagulation is performed under dry retinal conditions following a combination of intravitreal anti-VEGF or steroid injection with prompt or deferred focal laser treatment. In our study, 6 of 25 eyes (24%) received intravitreal anti-VEGF or steroid injection with prompt navigated focal laser treatment. Although there was no significant difference in retreatment rate of navigated laser photocoagulation with or without pretreatment of pharmacotherapy, it might be important to establish ideal protocol for treating thickened macular edema by Navilas laser system in future.

In addition, the MAs associated with DME were mainly found in deep capillary plexus of retina based on the OCT angiography (OCTA) [30]. Although OCTA cannot be used to visualize leakage, it is noninvasive, nondye imaging modality. In our study, only one eye was treated with OCTA-guided NAVILAS focal laser for the MAs located in deep capillary plexus, and we hope to study more number of eyes with OCTA-guided navigated focal laser in future.

There are several limitations to our current study. Because this study was a retrospective study, the additional intervention protocols, which were additional laser photocoagulation, anti-VEGF therapy, or steroid therapy, were not determined. This study was a nonrandomized study with no control groups and had relatively small number of patients and short follow-up period. Larger number and longer follow-up study would be warranted to study the efficacy of navigated focal laser photocoagulation for DME in future.

5. Conclusions

In conclusion, our study shows a significant decreasing of macular thickness using navigated laser photocoagulation based on multimodal imaging.

Conflicts of Interest

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

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Research Article

Less Expansion of Short-Pulse Laser Scars in Panretinal Photocoagulation for Diabetic Retinopathy

Masahiko Higaki, Miho Nozaki, Munenori Yoshida, and Yuichiro Ogura

Department of Ophthalmology and Visual Science, Nagoya City University Graduate School of Medical Sciences, Nagoya 467-8601, Japan

Correspondence should be addressed to Miho Nozaki; miho.nozaki@gmail.com

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Purpose. To compare the expansion rates of laser photocoagulation scars between the conventional laser and short-pulse laser using fundus autofluorescence (FAF). *Methods*. Retrospective chart review. Conventional laser was performed on 6 eyes of 6 patients, and short-pulse laser was performed on 11 eyes of 8 patients with diabetic retinopathy. FAF images were obtained by Optos® 200Tx (Optos, Dunfermline, Scotland, UK) at 1, 3, 6, and 12 months after treatment. The average area of 20 photocoagulation scars was measured by using ImageJ software. The expansion rates were calculated from the proportion of the averaged area against the optic disc area. Regression of retinopathy and central macular thickness were also evaluated. *Results*. The expansion rates of the conventional laser scars compared with the size at 1 month after treatment were 1.12 ± 0.08 (3 M), 1.27 ± 0.12 (6 M), and 1.39 ± 0.11 (12 M). The expansion rates of the short-pulse laser scars were 1.04 ± 0.05 (3 M), 1.09 ± 0.04 (6 M), and 1.13 ± 0.05 (12 M). The expansion rates of the short-pulse laser were significantly lower than those of the conventional laser ($p < 0.01$). *Conclusion*. FAF images were useful to evaluate the changes in the photocoagulation scar sizes. The scars with the short-pulse laser showed lower expansion rates than those of the conventional laser.

1. Introduction

Diabetic retinopathy is the leading cause of blindness in the working population of the Western world [1]. Although panretinal photocoagulation (PRP) is the standard therapy for reducing the activity of diabetic retinopathy [2], PRP sometimes results in decreased visual acuity due to PRP-induced macular edema [3–5]. Recently, short-pulse pattern scan laser system (PASCAL® Streamline, Topcon Medical Laser systems, Santa Clara, CA, USA) has been developed [6, 7], and it is known that short-pulse laser treatment is quicker, generates less heat, and is less painful to eyes than the conventional laser treatment [6]. Moreover, some reports indicate that short-pulse laser treatment induces less inflammation, fewer inflammatory cytokines in the sensory retina, and less macular thickening in patients with diabetic retinopathy than the conventional pulse duration [2–4, 8, 9].

Despite these advantages of the short-pulse laser, some studies indicate that short-pulse laser is less effective than the conventional laser treatment in treatment for the high-risk proliferative diabetic retinopathy. They suggested that the reason for the differences was that the total area of PRP scars generated by the conventional laser exceeded that of short-pulse laser although both groups were treated with the same number of laser spots [5, 10]. The photocoagulation scars performed by the conventional laser have a tendency to expand after treatment [5, 8, 11–14]. However, some reports revealed that the expansion rate of photocoagulation scars performed by the short-pulse laser is lower than that of the conventional laser [8, 12, 15]. In these reports, the laser scars were evaluated by using examination including color fundus photographs, fluorescein angiograms, and infrared images [8, 12] or OCT [16].

FAF imaging is a noninvasive technique used to assess retinal pigment epithelial (RPE) cells and now widely used to evaluate age-related macular degeneration [17], retinitis pigmentosa [18], and other chorioretinal diseases. FAF signals increase with lipofuscin accumulation in RPE cells and

decrease with RPE atrophy [19]. Analysis of FAF is an effective method to observe the functions of the RPE cells. Since retinal laser photocoagulation targets to RPE, FAF analysis after laser photocoagulation is thought to be an effective method to evaluate the RPE alterations and efficacy of laser photocoagulation. Although Muqit et al. already evaluated laser photocoagulation scars using FAF, they compared the FAF changes between the conventional laser and short-pulse laser only for 4 weeks [15], or they only followed FAF changes of 2 cases treated with short-pulse laser PRP [16].

In this study, we aimed to compare the FAF changes between the conventional laser and short-pulse laser in treatment of diabetic retinopathy, in terms of laser scar expansion rates and disease regression for 12 months.

2. Methods

This study was a retrospective cohort study. This study was approved by the Institutional Review Board of Nagoya City University Graduate School of Medical Science, conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki.

All patients were treated at Nagoya City University Hospital between September 2013 and February 2015. All patients were followed for at least 12 months after laser photocoagulation. The patients with media opacities such as corneal opacity, cataract, and vitreous hemorrhage, which may influence the FAF images, were excluded.

We evaluated the best corrected visual acuity (BCVA), the central macular thickness (CMT) in OCT (Cirrus HD-OCT 4000, Carl Zeiss Meditec, Dublin, CA, Germany), the regressions of neovascularization, and the expansion of photocoagulation scars in 17 eyes of 12 patients with diabetic retinopathy (PDR; 5 eyes, NPDR; 12 eyes).

The BCVA was measured with a Japanese standard decimal visual acuity chart, and decimal BCVA was calculated using the logarithm of the minimum angle of resolution (logMAR) scale.

FAF images were taken by Optos 200Tx at 1, 3, 6, and 12 months after treatment. We measured the pixel sizes of an optic disc and 20 laser scars near the vascular arcade on each visit using the digital image analysis software ImageJ (developed by Wayne Rasband, National Institutes of Health, Bethesda, MD, USA; available at http://rsb.info.nih.gov/ij/index.html) (Figures 1 and 2) and calculated the expansion rates from the proportions of the average area of laser scars against the optic disc area. All the measurements were performed twice by one investigator (Masahiko Higaki's visual inspection on clopped magnified images). Results were obtained by analyzing the mean values of the two measurements. The intraclass correlation coefficient (ICC, %) was also calculated to evaluate reproducibility.

The regressions of neovascularization were evaluated by fluorescein angiography (FA). FA was performed 6 months and 12 months after treatment to evaluate the efficacy of photocoagulation, and if there were any residual nonperfusion area or neovascularization, additional laser photocoagulation was applied.

2.1. Statistics. All results are expressed as the mean ± standard deviation. Differences in genders and severity of diabetic retinopathy were analyzed by the Fisher's exact test. Comparisons of age, BCVA, CMT, timing of additional laser, and the duration of follow-up were performed using the Student's t-test. Expansion rates were analyzed using repeated measure ANOVA. The number of PRP shots was compared with Mann–Whitney U test. In all analyses, $p < 0.05$ was considered to be statistically significant. Statistics were calculated using Statcel 3 statistical software, version 3 (OMS Inc., Saitama, Japan).

3. Results

3.1. Patient Characteristics. The laser treatment was performed with the conventional laser (Novus Varia, Lumenis, Santa Clara, CA, USA) in 6 eyes and the short-pulse laser (PASCAL Streamline) in 11 eyes. Clinical characteristics of the patients are shown in Table 1. Conventional laser group included 3 PDR eyes, and short-pulse laser group included 2 PDR eyes. Although the conventional laser group included more PDR eyes, there was no statistically significant difference.

The mean age of patients was 65.8 ± 8.3 (range: 53–77) years old in the conventional laser group and 55.0 ± 14.1 (range: 34–77) years old in short-pulse laser group. The mean follow-up period was 15.5 ± 3.6 (range: 12–21) months in the conventional group and 16.6 ± 3.7 (range: 12–24) in short-pulse laser group. There were no statistically significant differences in age and follow-up period between the two groups. And all phakic patients did not receive cataract surgery during the follow-up period.

3.2. Laser Setting Parameters. Both laser methods were performed in the same spot size (200 μm) at different power to attain gray-white burn with Mainster PRP 165 contact lens (Ocular Instruments Inc., Bellevue, WA, USA). Yellow wavelength (577 nm) was used in both modalities. Sub-Tenon's triamcinolone acetonide (Kenacort; Bristol-Myers Squibb, Tokyo, Japan) injections (STTA) were performed after the first session of laser treatment (4 eyes in the conventional laser group and 2 eyes in the short-pulse laser group). The summary of the settings used in the conventional laser and the short-pulse laser was shown in Table 2. One eye in the conventional laser group was previously treated with targeted retinal photocoagulation (TRP) [20]. In the short-pulse laser group, 4 eyes were treated with TRP, and 3 eyes were previously treated with TRP. Other 4 eyes were treated with PRP. The mean PRP number of laser shots performed in the treatment-naive eye was 1798 ± 885 in the conventional laser group and 4247 ± 279 in short-pulse laser group, and there was a significant difference ($p < 0.05$, Mann–Whitney U test).

3.3. The Best-Corrected Visual Acuity. The mean BCVA (logMAR) before the conventional laser treatment was 0.64 ± 0.41 and 0.35 ± 0.44 at 12 months after treatment. The mean BCVA before the short-pulse laser treatment was −0.05 ± 0.12 and 0.00 ± 0.13 at 12 months after

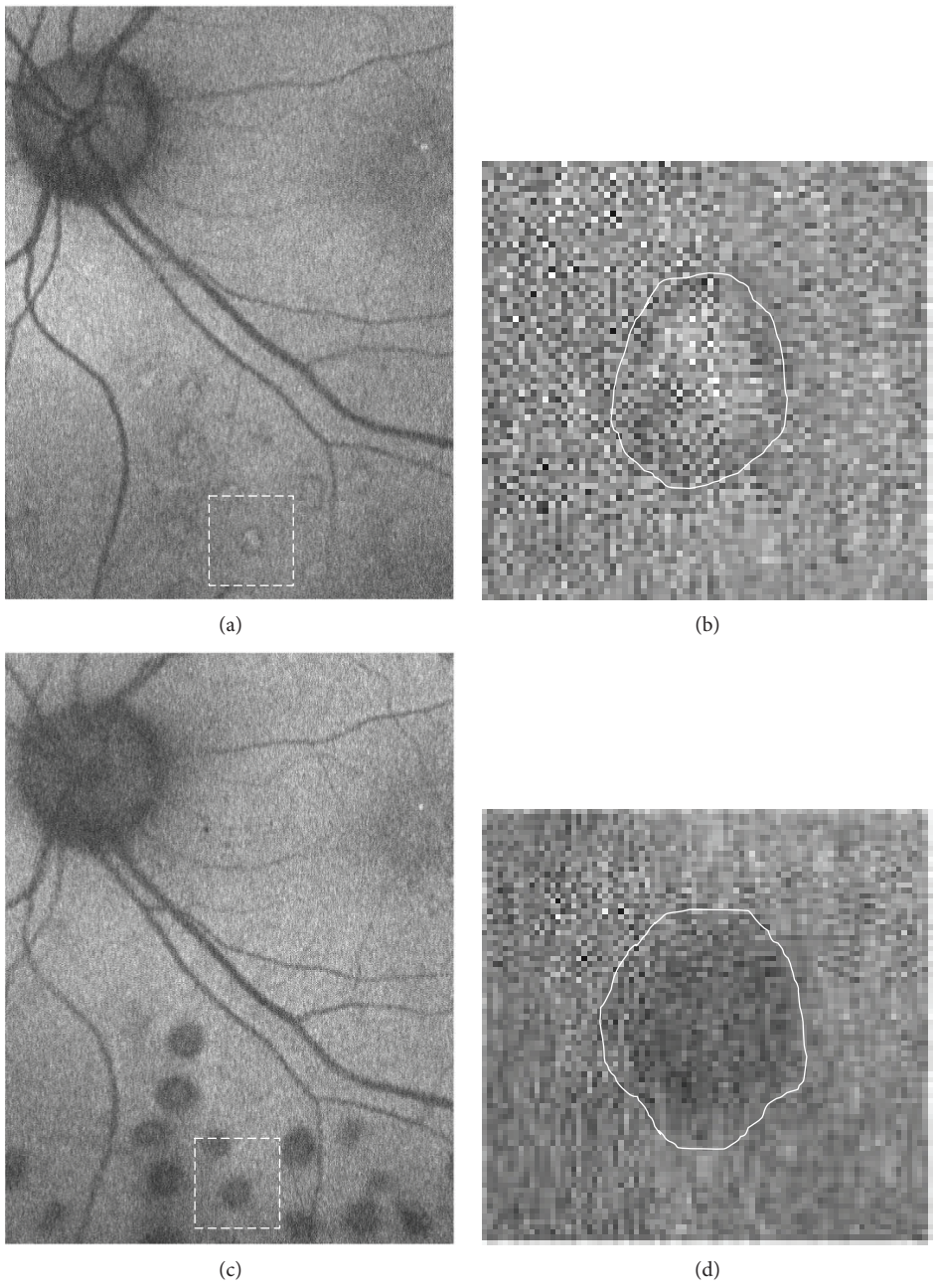

Figure 1: Representative images of fundus autofluorescence (FAF) in the conventional laser group. The images were taken 1 month after laser treatment (a, b) and 12 months after treatment (c, d). Twenty laser scars near the vascular arcade were measured using the digital image analysis software ImageJ on each visit. Higher magnification of the area surrounded by white-dashed line was shown in (b) and (d). White line indicated the outline of FAF laser scars for measurement (b, d). High magnification images show the changes of laser scars from hyperautofluorescent at 1 months (b) to hypoautofluorescent at 12 months after laser treatment (d).

treatment. There was no significant aggravation of BCVA 12 months after treatment in both groups.

3.4. Central Macular Thickness (CMT). The mean CMT before the conventional laser treatment was $339.6 \pm 80.0\ \mu$m, and the mean CMT at 12 months after treatment was $329.0 \pm 81.0\ \mu$m. The mean CMT before the short-pulse laser treatment was $266.5 \pm 35.4\ \mu$m and that at 12 months after treatment was $272.1 \pm 32.3\ \mu$m. There was no significant aggravation of CMT 12 months after treatment in both groups.

3.5. Disease Regression Outcomes. In the conventional laser group, two eyes (33%) required additional laser due to the residual nonperfusion area (9 or 13 months after treatment). Two eyes (33%) were treated additionally due to residual nonperfusion area and neovascularization (7 or 13 months after treatment). And one eye (14%) developed macular edema 4 months after laser treatment, and focal laser photocoagulation was performed using Navilas laser system (OD-OS GmbH, Teltow, Germany). This patient was previously treated by several injections of antivascular endothelial

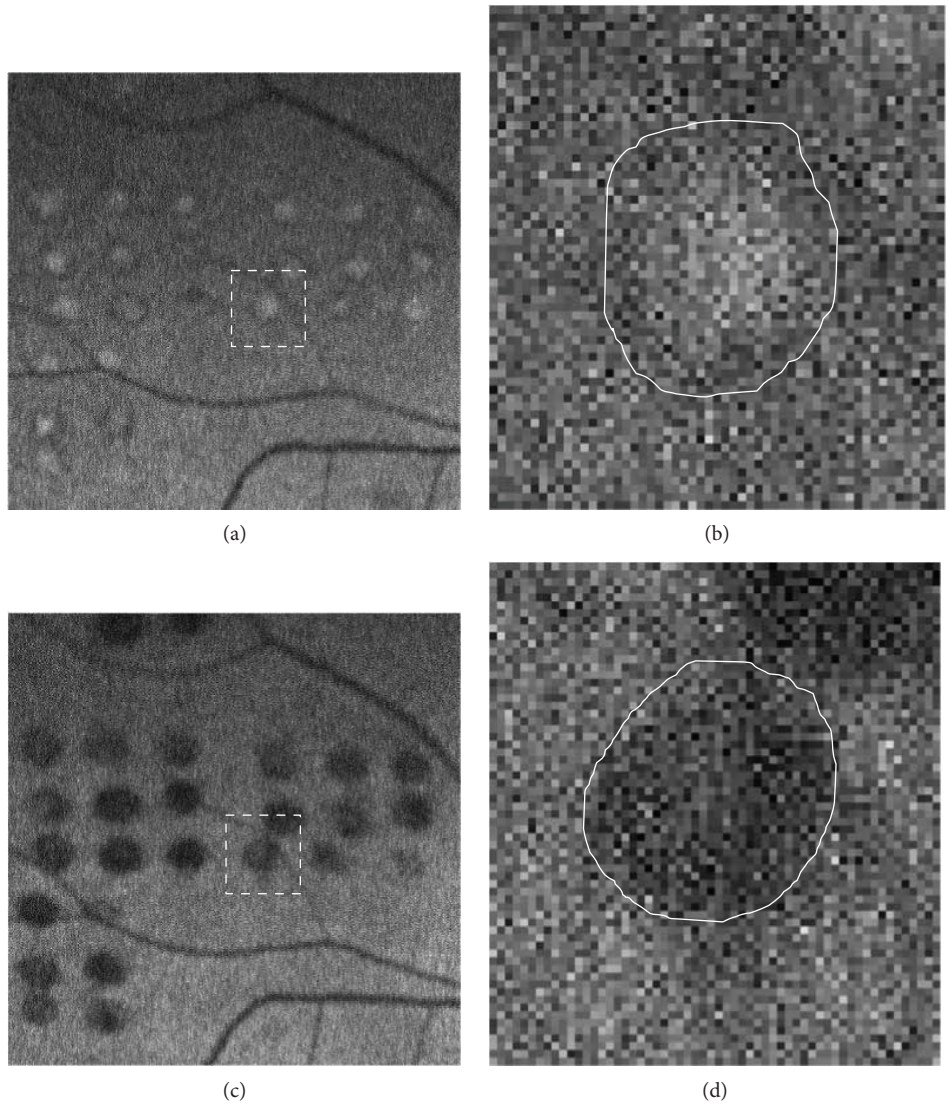

Figure 2: Representative images of FAF in the short-pulse laser group. The images were taken 1 month after laser treatment (a, b) and 12 months after treatment (c, d). Twenty laser scars near the vascular arcade were measured using the digital image analysis software ImageJ on each visit. Higher magnification of the area surrounded by white-dashed line was shown in (b) and (d). White line indicated the outline of FAF laser scars for measurement (b, d). High magnification images show the changes of laser scars from hyperautofluorescent at 1 month (b) to hypoautofluorescent at 12 months after laser treatment (d).

growth factor (VEGF) for diabetic macular edema (DME). At the time when PRP was given, DME was resolved, and she was not treated with STTA.

In the short-pulse laser group, 4 eyes (36%) received additional laser due to the residual nonperfusion area (6–9 months after treatment). One eye developed retinal break with posterior vitreous detachment, and the laser photocoagulation was performed around the retinal break (5 months after treatment). One eye (9%) showed recurrence of macular edema 7 months after laser treatment, and focal laser photocoagulation was performed. This patient was treated with STTA when PRP was given (4411 shots in one session).

The timing of additional laser showed no significant difference between both groups.

3.6. Photocoagulation Scar Expansion. We measured the size of 20 laser scars near the vascular arcade on each visit and calculated the expansion rate over time. The intraclass correlation coefficient (ICC, %) was evaluated (Table 3). Based on these results, the collected data were considered to be reliable and useful for further analysis.

The expansion rates of scars with the conventional laser were 1.12 ± 0.08 (3 M), 1.27 ± 0.12 (6 M), and 1.39 ± 0.11 (12 M) (Figures 3 and 4).

On the other hand, the expansion rates of scars with the short-pulse laser against the scar size in 1 month after treatment were 1.04 ± 0.05 (3 M), 1.09 ± 0.04 (6 M), and 1.13 ± 0.05 (12 M) (Figures 3 and 4).

As a result, the expansion rates of both groups increased significantly over time ($p < 0.01$) and the expansion rates of

Table 1: Patient characteristics.

	Conventional laser	Short-pulse laser	p
Number of eyes	6	11	
Mean age, years	65.8 ± 8.3	55.0 ± 14.1	0.13†
Male : Female	4 : 2	5 : 3	0.65‡
NPDR : PDR	3 : 3	9 : 2	0.29‡
Duration of follow-up (months)	15.5 ± 3.6	16.6 ± 3.7	0.58†
BCVA (logMAR) pretreatment	0.64 ± 0.41	−0.05 ± 0.12	<0.01†
BCVA (logMAR) posttreatment (12 M)	0.35 ± 0.44	0.00 ± 0.13	<0.05†
Mean CMT pretreatment (μm)	339.6 ± 80.0	266.5 ± 35.4	<0.05†
Mean CMT post- treatment (μm) (12 M)	329.0 ± 81.0	272.1 ± 32.3	0.08†
Phakic eyes : pseudophakic eyes	3 : 3	10 : 1	0.10‡
Number of operators	5	5	
STTA	4	2	0.07‡

†Student's t-test; ‡Fisher's exact test. NPDR: nonproliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; BCVA: best-corrected visual acuity; CMT: central macular thickness; STTA: sub-Tenon's injections of triamcinolone acetonide.

Table 2: Settings of laser treatment.

	Conventional laser	Short-pulse laser	p
Power (mW)	100–260	300–500	—
Pulse duration (ms)	200	20	—
Spot size (μm)	200	20	—
Wavelength (nm)	Yellow (577)	Yellow (577)	—
Spacing (spot)	1	0.75	—
Mean number of total PRP shots (in treatment naive eyes)	1798 ± 885 (958–3505)	4247 ± 279 (3875–4600)	<0.05†

†Mann–Whitney U test. PRP: panretinal photocoagulation.

Table 3: Intraclass correlation coefficient.

	Conventional group		Short-pulse group	
	M1	M2	M1	M2
Mean scar area divided by disc area, month 1	0.072 ± 0.010	0.074 ± 0.009	0.037 ± 0.040	0.038 ± 0.003
Mean of M1 and M2	0.073 ± 0.009		0.037 ± 0.004	
ICC, %	81.6		79.2	
Mean scar area divided by disc area, month 3	0.081 ± 0.013	0.081 ± 0.012	0.039 ± 0.004	0.040 ± 0.004
Mean of M1 and M2	0.081 ± 0.013		0.040 ± 0.004	
ICC, %	88.3		81.1	
Mean scar area divided by disc area, month 6	0.093 ± 0.012	0.093 ± 0.011	0.041 ± 0.004	0.041 ± 0.004
Mean of M1 and M2	0.093 ± 0.011		0.041 ± 0.004	
ICC, %	87.0		87.3	
Mean scar area divided by disc area, month 12	0.102 ± 0.017	0.102 ± 0.016	0.043 ± 0.003	0.043 ± 0.003
Mean of M1 and M2	0.102 ± 0.016		0.043 ± 0.003	
ICC, %	83.5		84.1	

M1: measurement 1; M2: measurement 2. ICC: intraclass correlation coefficient.

short-pulse laser scars were significantly lower than those of conventional laser scars over time ($p < 0.01$) (Figure 3). There were 5 operators in each group, and there were no significant differences in expansion rates among operators.

3.7. FAF Findings. The conventional laser scars changed from hyperautofluorescent to hypoautofluorescent more rapidly than the short-pulse laser scars (Figure 4). All the photocoagulation scars in both groups were hyperautofluorescent at month 3 (Figures 4(a)–4(c)). The photocoagulation scars in the conventional laser group became hypoautofluorescent in 5 out of 6 eyes (83.3%) at month 6 (Figure 4(b)) and 6 out of 6 eyes (100%) at month 12. On the other hand, the photocoagulation scars in the short-pulse laser group became

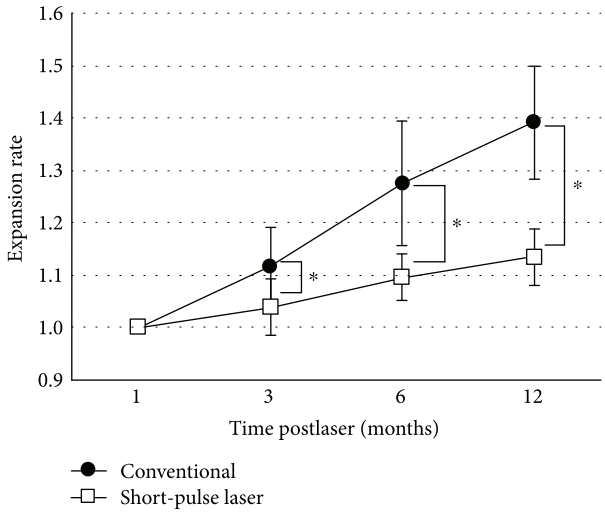

Figure 3: Expansion rates of laser scars with the conventional laser (closed circle) and short-pulse laser (open square) in months 3, 6, and 12 after laser treatment. Laser scars significantly expanded in both modalities, and the expansion rates of the short-pulse laser were significantly lower than those of conventional laser scars. Repeated measure ANOVA,$^*p < 0.01$.

hypoautofluorescent in 1 out of 11 eyes (9.1%) at month 6 (Figure 4(d)) and 7 out of 11 eyes (63.6%) at month 12. There was no relationship between FAF changes and laser augmentations. The FAF findings were all similar among operators.

4. Discussion

Our study showed that the laser photocoagulation scars kept growing for 12 months; however, the expansion rates of the short-pulse laser scars were significantly lower than those of the conventional laser scars during the period of observation. We used noninvasive FAF images taken by Optos 200Tx. By using FAF images, we were able to measure the sizes of photocoagulation scars easily due to their sharp outlines [15, 16].

These results were consistent with the following two previous reports. According to Nagpal et al., the expansion rate of the conventional laser was 27.2% and that of the short-pulse laser was 14.0% three months after laser treatment [8]. Shiraya et al. showed us that the expansion rate of the conventional laser was 18% and that of the short-pulse laser was 14% six months after laser photocoagulation [12].

On the other hand, some reports indicated that the 20-millisecond-pulse burns progressively reduced in size after photocoagulation [9, 15, 16, 21]. It can be surmised that the early retinal edema decreased with the lapse of time in these reports. Therefore, we set the values in one month after laser treatment as a benchmark to avoid the effect of the early retinal edema.

When the conventional laser is performed, photoreceptors usually suffer damage although the main target is RPE. Photoreceptors connect with adjacent photoreceptors through horizontal or amacrine cells. After local photoreceptors undergo necrosis, it causes apoptosis of the surrounding photoreceptors subsequently. As a consequence, photocoagulation scars expand [11, 22]. In contrast, when the short-pulse laser is performed, the retinal damage is mostly confined to the outer retina because its pulse duration is very short (10–30 ms) [16, 21, 22]. Accordingly, photoreceptors suffer much less damage and the photocoagulation scars enlarge less than the conventional laser as a result.

In this FAF study, the short-pulse laser scars changed from hyperautofluorescent to hypoautofluorescent more slowly than the conventional laser scars. In the short-pulse laser group, all 4 eyes followed by 18 months showed hypoautofluorescent scars. This is possibly because of the chorioretinal damage by the short-pulse laser is confined to the outer retina. Conventional laser induces choriocapillaris atrophy which accelerates death of RPE and photoreceptors [23] and accelerated death of RPE and photoreceptors resulted in reduced FAF signal [19].

These results should be considered when laser photocoagulation therapy is performed for patients who have diabetic retinopathy or other retinal diseases. A report indicated that PRP performed by the short-pulse laser is less effective than that performed by the conventional argon laser in regression of neovascularization or incidence of vitreous hemorrhage within 6 months after treatment when the same number of spots was applied [5]. It is possible to deduce that the total area of PRP scars in the argon-treated patient exceeds that of the patient who underwent the short-pulse laser [10], and we should also consider the variability of photocoagulation lesions between physicians and patients [24], although there were no differences in expansion rates among operators in this study. Therefore, it is important for an operator to reconsider the settings of treatment parameters when using short-pulse laser therapy for serious retinal diseases such as high-risk PDR [5]. In this study, we set spacing as 0.75, and the total number of laser spots for PRP is significantly higher in the short-pulse laser group, and during this study follow-up period, no eye developed new vitreous hemorrhage in both groups during this study. Although the number of eyes with PDR was higher in the conventional laser group, suitable space setting (0.75) and higher number of laser spots might result in successful PRP.

As for PRP-induced macular edema, there were no significant differences in CMT before and after laser photocoagulation both in the conventional laser and short-pulse laser group in this study. STTA before PRP has been known as an effective treatment to prevent from PRP-induced macular edema [25], and we usually employ STTA when we start PRP in the eyes with already existing macular edema. However, one eye developed macular edema after PRP in the conventional laser group. She had past history of DME treated with multiple injections of anti-VEGF, but she did not receive STTA when PRP was given because macular edema was resolved at that time. But her parafoveal retinal thickness was 372 μm when PRP was initiated. Shimura et al. reported that patients whose preoperative parafoveal thickness was >300 μm had a worse visual prognosis due to PRP-induced macular edema [26]. From this background, this eye also should have been treated with STTA when PRP was given. Conversely, one eye also showed recurrence of macular edema after PRP in the short-pulse group 7 months after treatment, and he was treated with STTA when

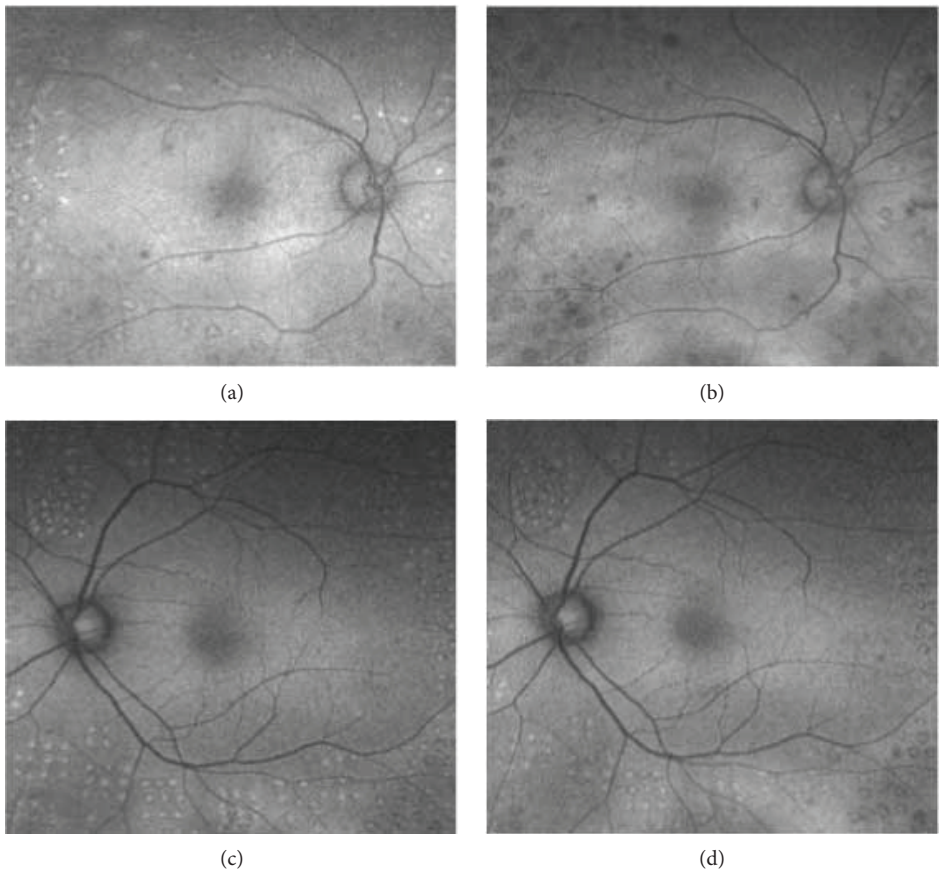

Figure 4: Representative images of FAF in the conventional laser group (a, b) and short-pulse laser group (c, d). The images were taken 3 months after laser treatment (a, c) and 6 months after laser treatment (b, d). Three months after laser treatment, the laser scars showed an increased level of autofluorescence (AF) surrounded by a decreased level of AF in both groups (a, c). Six months after laser treatment, the laser scars in the conventional laser group changed to hypoautofluorescent (b). However, in the short-pulse laser group, laser scars did not change to hypoautofluorescent (d).

PRP was given (4411 shots). From the overall results, there was no difference in terms of regression of retinopathy and worsening of macular edema between the conventional laser group and short-pulse laser group in our study.

There were several limitations that need to be acknowledged in our current study. First, there was a relatively small number of eyes with nonrandomized, retrospective methods. To compare the efficacy and expansion rate with the short-pulse laser and conventional laser, a large number of study with randomization will be warranted. Second, we used the wide-field imaging system, but we adopted only the postpole area. The reason was because the magnification of the posterior pole and that of midperiphery was different when using the images of Optos 200Tx [27]. Moreover, laser photocoagulation scars enlarge more in the posterior pole area than in the peripheral area [11]. Taking these differences into consideration, we decided to adopt the photocoagulation scars to evaluate only in the area of the posterior pole. Recently, the new software using stereographic projection, in which the lesion areas on ultra-wide-field images can be calculated in anatomically correct physical units (mm^2), has been developed [28]. Nevertheless, this software is not commercially available yet, we believe that the total area of laser scar evaluation using FAF will give us more useful information of efficacy on laser photocoagulation in the future.

5. Conclusion

FAF imaging was useful to evaluate the temporal changes in the laser photocoagulation scar size. The scars with the short-pulse laser consistently showed lower expansion rates compared with those of the conventional laser. The change in CMT between the two groups was not significant.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

A preliminary version of this paper was presented at the 9th Congress of Asia-Pacific Vitreo-retina Society meeting in Sydney, 2015.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Research Article

Comparison of Intravitreal Aflibercept and Ranibizumab following Initial Treatment with Ranibizumab in Persistent Diabetic Macular Edema

Ali Demircan, Zeynep Alkin, Ceren Yesilkaya, Gokhan Demir, and Burcu Kemer

Beyoglu Eye Research and Training Hospital, Istanbul, Turkey

Correspondence should be addressed to Ali Demircan; alidemircanctf@yahoo.com

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Purpose. To compare the visual and anatomic outcomes in patients with persistent diabetic macular edema (DME) who switched from ranibizumab to aflibercept with those who continued with previous ranibizumab therapy. *Methods*. In this retrospective comparative study, medical records of consecutive patients with center-involved DME ≥ 350 μm who had at least three recent consecutive monthly ranibizumab injections followed by as-needed therapy with either aflibercept or ranibizumab were reviewed. Data were collected at presentation (preinjection), at the intermediary visit, and at the last visit (at the end of the follow-up period). *Results*. Forty-three eyes of 43 patients were divided into two groups: the switch group ($n = 20$) and the ranibizumab group ($n = 23$). Though no significant improvement was found in the mean BCVA from the intermediary visit to the last visit, there was a difference in the mean CMT in the switch group and the ranibizumab group ($p < 0.001$ and $p = 0.03$, resp.). The mean CMT decreased after the intermediary visit by 188.6 ± 120.5 μm in the switch group and by 60.3 ± 117.1 μm in the ranibizumab group ($p = 0.003$). *Conclusions*. Both aflibercept and ranibizumab decreased CMT in patients with persistent DME who showed a poor response to ranibizumab injections. However, switching to aflibercept provided only morphologic improvement.

1. Introduction

Diabetic retinopathy is the leading cause of visual impairment among working-age people aged <45 years around the world and is rising in prevalence [1, 2]. Diabetic macular edema (DME) leads to visual impairment in diabetic retinopathy, and its prevalence has been estimated as 6.8% in the diabetic population [3]. Currently, clinical trials providing level 1 evidence have revealed that antivascular endothelial growth factor (VEGF) agents, United States Food and Drug Administration-approved ranibizumab and aflibercept, as well as off-label bevacizumab, are the most effective treatment options for improvement of visual acuity and macular morphology for center-involving DME compared with laser [4–6]. The RISE-RIDE trials for ranibizumab, VIVID-VISTA trials for aflibercept, and numerous studies with level 2 and 3 evidence for bevacizumab demonstrated that almost 40% of patients gained 15 letters or more on Snellen eye charts at two years of follow-up [4–8]. Although a significant proportion of patients had visual and anatomic improvement in prospective multicenter studies with regular treatment and follow-up schedules, a considerable amount of patients showed poor response to current anti-VEGF treatment. Hence, it is logical to switch anti-VEGF agents between each other if the previous treatment is not sufficient to resolve macular edema. However, few studies have assessed the results of switching anti-VEGF therapies in patients with poor response to DME [9–12]. In light of these findings, there is still a question that remains to be answered regarding whether macular edema resolves when previous treatment is continued. To date, there are limited data about switching anti-VEGF agents regarding their effectiveness in DME. The aim of this study was to address the outcomes of aflibercept use in patients who did not respond to previous ranibizumab treatment. Therefore, the visual and anatomic outcomes of switching therapy from

ranibizumab to aflibercept were compared with those of patients treated with ranibizumab only in persistent/non-resolving macular edema secondary to diabetes.

2. Methods

In this retrospective, observational, comparative case series, data were collected from the records of sequential patients who were followed up for DME. To identify eligible patients who were both treated with ranibizumab injections (0.5 mg/0.05 mL) continuously and previously treated with ranibizumab and were subsequently switched to aflibercept (2 mg/0.05 mL), electronic medical records of patients with DME between August 2015 and May 2017 were reviewed. Written informed consent was obtained from all patients before the injections, and the protocol of the study adhered to the tenets of the Declaration of Helsinki.

To be included in the study, each patient was required to meet all of the following criteria: patients with type 2 diabetes aged ≥18 years, center-involving DME (central macular thickness (CMT) ≥ 350 μm), and best corrected visual acuity (BCVA) of ≥20/400. Patients were excluded if they had any of the following treatments within 6 months prior to study entry: intravitreal or sub-Tenon's injections of steroids, intravitreal dexamethasone implant, intravitreal anti-VEGF injections, focal/grid macular laser photocoagulation, panretinal photocoagulation, cataract surgery, or pars plana vitrectomy. Patients who had macular edema secondary to a cause other than diabetes or any concomitant ocular pathologies aside from diabetic retinopathy or vitreoretinal surface disorders were also excluded.

Afterwards, the patients ($n = 43$) were divided into two groups: the switch group ($n = 20$) consisted of patients who demonstrated poor response or an increase in CMT after the last three monthly ranibizumab injections following former ranibizumab treatment and then switched to aflibercept and the ranibizumab group ($n = 23$) comprised patients who demonstrated a poor response (decrease in CMT < 10%) after the last three monthly ranibizumab injections following former ranibizumab treatment and then continued to receive ranibizumab injections.

In the presence of persisting subretinal or intraretinal fluid, treatment with ranibizumab or aflibercept was continued using an as-needed regimen until no improvement in CMT was seen.

The decision to treat using an as-needed regimen, which followed an optical coherence tomography- (OCT-) guided treatment protocol, was made by a retina specialist. If no center-involved macular edema was seen, monthly monitoring visits were arranged and further injections of ranibizumab or aflibercept were withheld. In case of newly formed or persistent macular edema or increase in CMT ≥ 50 μm compared with the previous visit, retreatment with either intravitreal ranibizumab or aflibercept was applied.

At each visit, a complete ophthalmologic examination including measurement of BCVA using Snellen charts, slit-lamp biomicroscopy, intraocular pressure measurement using applanation tonometry, and dilated biomicroscopic fundus examination was conducted and OCT imaging using a SPECTRALIS OCT (SPECTRALIS; Heidelberg Engineering, Heidelberg, Germany) was performed. Data were collected at presentation (preinjection), at the intermediary visit (preswitch visit in the switch group and 4–6 weeks after the last injection of three monthly ranibizumab injections in the ranibizumab group), and at the last visit (at the end of the follow-up period). Only data of patients who completed a minimum 6-month follow-up period after the intermediary visit were collected for analysis.

CMT, which is defined as the mean thickness of the neurosensory retina in the central 1 mm diameter, was computed through OCT mapping software provided by the device. OCT characteristics of DME were classified as cystoid macular edema (CME), serous retinal detachment (SRD), and sponge-like retinal swelling [13]. CME associated with or without sponge-like retinal swelling was classified as CME. The presence of disorganization of inner retinal layers (DRIL) and disruption of the ellipsoid zone (EZ) (formerly termed inner segment/outer segment photoreceptor junction) were evaluated on the central B scan which was identified as the central scan passing through the central foveal area on the infrared image. DRIL was defined as any irregularity obscuring the well-delineated boundaries between the inner retinal layers (the ganglion cell-inner plexiform layer complex, inner nuclear layer, and outer plexiform layer). Foveal 1 mm zone was evaluated for the presence of DRIL and disruption of EZ. If ≥50% of the central foveal 1 mm zone was affected by DRIL, then DRIL was considered as present according to a previous study [14]. If EZ was disrupted within the 1 mm foveal area, EZ was graded as not intact [15]. B scans were evaluated by two independent specialists (Ali Demircan and Zeynep Alkin). The observed agreement between the 2 graders was 92.7%. All disagreement scans were resolved by mutual agreement.

The demographic features of patients at baseline, BCVA and CMT values obtained at all visits, and the mean number of anti-VEGF injections at the first and last visits were recorded. The mean changes in CMT and BCVA from baseline at the last visit were the primary outcomes and were used to compare the efficacy of both treatments. The percentage of patients who gained ≥1 line in BCVA, with CMT < 350 μm at the last visit, and with ≥10% reduction in CMT were secondary outcomes.

2.1. Statistical Analysis. Data were analyzed using SPSS 22.0 program (SPSS Chicago, Illinois, USA). Snellen BCVA was converted into logarithm of the minimal angle of resolution (logMAR) for statistical analysis. Continuous variables are expressed as mean ± standard deviation (SD). Categorical variables are expressed as numbers (n) and percentages (%). The distribution of the variables was measured using the Kolmogorov–Smirnov test. The Mann–Whitney U test was used for the analysis of independent quantitative data. The Wilcoxon test was used for the analysis of dependent quantitative data. The chi-square test was used to analyze independent qualitative data, and Fisher's exact test was used when chi-square test conditions were not met. Spearman's correlation analysis was used for correlation analyses.

3. Results

A total of 43 eyes of 43 patients were included; these comprised both patients who switched from ranibizumab to aflibercept (switch group, $n = 20$) and those treated with ranibizumab only (ranibizumab group, $n = 23$). The mean age was 62.1 ± 7.5 years in the switch group and 63.4 ± 6.5 years in the ranibizumab group. No significant difference was found between the groups ($p = 0.37$). The demographics and clinical characteristics of the patients in both groups are shown in Table 1.

The mean BCVA (logMAR) in the switch and ranibizumab groups was 0.67 ± 0.38 (range: 1.3–0.2) and 0.73 ± 0.34 (range: 1.3–0.15), respectively, at presentation. No statistically significant difference was found between the groups ($p = 0.55$). In the switch group, the mean BCVA (logMAR) improved from 0.68 ± 0.40 at the intermediary visit to 0.58 ± 0.38 at the last visit. Compared with the intermediary visit, there was no statistically significant improvement at the last visit ($p = 0.08$). In the ranibizumab group, the mean BCVA (logMAR) improved from 0.71 ± 0.37 at the intermediary visit to 0.67 ± 0.37 at the last visit; no significant difference was found at the last visit compared with the intermediary visit ($p = 0.12$).

The changes in the mean CMT of the two groups are shown in Figure 1. The mean CMT in the switch and ranibizumab groups was $506.9 \pm 102.2\,\mu$m (range: 360–707 μm) and $487.3 \pm 82.6\,\mu$m (range: 387–692 μm) at presentation and $530.7 \pm 91.8\,\mu$m and $473.5 \pm 78.4\,\mu$m at the intermediary visit. No statistically significant difference was found between the groups ($p = 0.53$, $p = 0.07$, resp.).

The mean CMT decreased from $530.7 \pm 91.8\,\mu$m and $473.5 \pm 78.4\,\mu$m at the intermediary visit to $342.1 \pm 87.5\,\mu$m and $413.2 \pm 123.8\,\mu$m at the last visit in the switch and ranibizumab groups, respectively. Compared with the intermediary visit, there was a significant decrease at the last visit in the switch and ranibizumab groups ($p < 0.001$ and $p = 0.03$ resp.). The mean CMT decreased after the intermediary visit by $188.6 \pm 120.5\,\mu$m in the switch group and by $60.3 \pm 117.1\,\mu$m in the ranibizumab group. A significant difference was found in CMT reduction between the switch group and the ranibizumab group ($p = 0.003$).

At the last visit, 5 of 20 eyes (25%) in the switch group and 4 of 23 eyes (17.3%) in the ranibizumab group showed a ≥1 line improvement in BCVA. The number of eyes with ≥10% reduction in CMT at the last visit was 18 of 20 eyes (90%) in the switch group and 11 of 23 eyes (47.8%) in the ranibizumab group. There were 12 of 20 eyes (60%) in the switch group and 7 of 23 eyes (34.7%) in the ranibizumab group in which CMT was <350 μm at the last visit.

At the intermediary visit, 20 of the 20 eyes (100%) in the switch group and 23 of the 23 eyes (100%) in the ranibizumab group had CME on OCT. SRD was present in 8 eyes (40%) in the switch group and 5 eyes (21.7%) in the ranibizumab group. Eight eyes (40%) in the switch group and 6 eyes (26%) in the ranibizumab group had the presence of DRIL. EZ disruption was present in 9 eyes (45%) in the switch group and 7 eyes (30.4%) in the ranibizumab group.

Table 1: Demographics and number of ranibizumab injections in both groups.

	Switch group $n = 20$	Ranibizumab group $n = 23$	p
Age (years)			0.37
Mean (±SD)	62.1 ± 7.5	63.4 ± 6.5	
Median (min–max)	60 (50–76)	64 (53–72)	
Gender			0.09
Male	9 (45%)	13 (56.5%)	
Female	11 (55%)	10 (43.4%)	
Number of ranibizumab injections before intermediary visit			0.64
Mean (±SD)	5.3 ± 1.2	5.5 ± 0.9	
Median (min–max)	5 (3–5)	5 (3–5)	

n: number; SD: standard deviation.

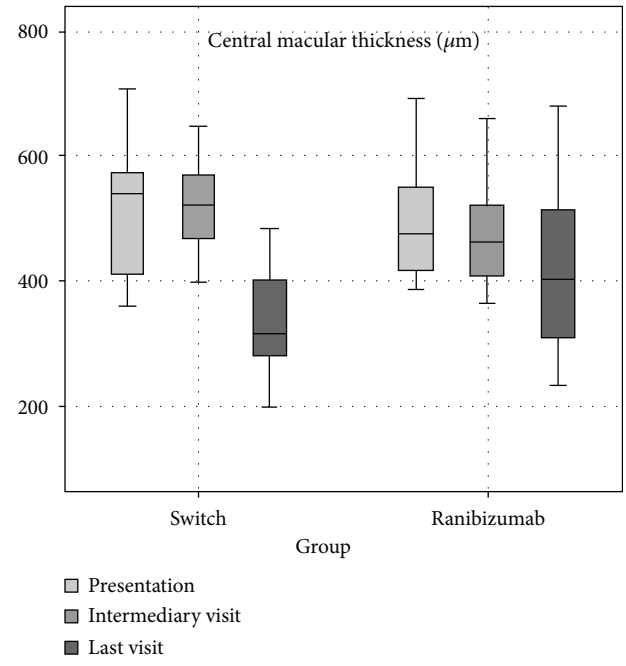

Figure 1

The mean number of ranibizumab injections was 5.3 ± 1.2 (range: 4–9) in the switch group and 5.5 ± 0.9 (range: 4–7) in the ranibizumab group before the intermediary visit in a mean period of 12 months. No statistically significant difference was found between the groups ($p = 0.64$). Eyes in the switch and ranibizumab groups received a mean number of 3.5 ± 0.7 (range: 3–5) and 3.7 ± 0.6 (range: 3–5) injections from the intermediary visit and the last visit, respectively, with a mean duration of 6.7 ± 0.8 months. There was no significant difference between the switch group and the ranibizumab group in the mean number of injections after the intermediary visit ($p = 0.32$).

4. Discussion

Vascular endothelial growth factor is an important mediator in the pathogenesis of DME. Intravitreal injections of anti-VEGFs have been established as the main treatment of DME in the last few years. In spite of regular treatment, there are a proportion of patients who incompletely respond to anti-VEGF agents. The Diabetic Retinopathy Clinical Research Network (DRCRnet) Protocol I showed that 52% of patients treated with ranibizumab failed to achieve ≥2 line improvement in BCVA and that 40% had no resolution of retinal thickening at the second year [16]. When treating DME with anti-VEGF agents, the physician has the option of trying other anti-VEGFs or corticosteroids in patients with poor response. Although there are no large randomized prospective clinical trials comparing treatment regimens for refractory DME, several smaller uncontrolled studies demonstrated visual and/or morphologic improvement after switching patients who showed poor response from aflibercept to ranibizumab injections [9–12].

Lim et al. reported visual and morphologic improvements after switching to aflibercept in 21 eyes of 19 patients with DME who had a poor response to multiple bevacizumab/ranibizumab injections [11]. A study by Bahrami et al. similarly demonstrated the beneficial effect of aflibercept on both visual improvement as well as morphologic improvement in patients with DME who had poor response to previous bevacizumab injections [17]. Wood et al. showed only morphologic improvement with aflibercept in patients with poor response to ranibizumab and/or bevacizumab injections in their prospective study [18]. However, the majority of patients (11 of 14) in their study were evaluated after only one aflibercept injection. Rahimy et al. also demonstrated only a morphologic response to aflibercept injections after previous bevacizumab/or ranibizumab therapy, and they explained this result by irreversible functional damage caused by long-standing DME [19]. Switching to aflibercept resulted in some anatomic improvement in the majority of patients in all studies.

In our study, both ranibizumab and aflibercept treatments provided only morphologic improvement in patients who have poor response to previous ranibizumab treatment. A greater decrease in macular thickness in the switch group than in the ranibizumab group in the current study might be explained by the blocking of all isoforms of VEGF-A, VEGF-B, and PlGF with aflibercept in contrast to inactivation of only VEGF-A with ranibizumab. Some studies showed that PlGF may have a place in the pathogenesis of DME. Increasing intravitreal concentrations of PlGF has been associated with progressively advancing degrees of diabetic retinopathy [20–23]. Blockade of this protein might play a role in such patients. Moreover, the greater improvement in macular morphology with aflibercept might be related to patients' inherent characteristics rather than features of aflibercept. In addition to all these possible explanations, patients treated with repetitive ranibizumab/bevacizumab injections may demonstrate tachyphylaxis or a diminished therapeutic response to these agents over time as suggested in a great number of studies [24, 25]. Additionally, there was a trend towards greater visual acuity improvement after switching to aflibercept, but it was not statistically significant. The discrepancy between morphologic and functional outcomes may be explained by irreversible functional damage caused by long-standing DME. Switching to intravitreal steroids with good functional and morphologic outcomes after ranibizumab failure in DME treatment has been shown in previous studies [26]. A switch to another pharmaceutical class such as corticosteroids is a logical option in case of failure of other therapies in DME.

All of the previous studies only reported outcomes of patients with a poor response to bevacizumab/ranibizumab who switched to aflibercept and had no comparison between the outcomes of switched patients and those of patients who continued with previous anti-VEGF treatment. It is not clear whether the visual and/or anatomic recovery in these patients originated from the new intravitreal anti-VEGF agent or from the total number of anti-VEGF injections applied because it was demonstrated that there was a delayed responder group treated with ranibizumab that showed some visual and anatomic improvement when treatment was continued with further ranibizumab injections.

The major limitations of this study were the relatively small sample size and short follow-up time as well as its retrospective design. Further prospective and randomized studies with larger sample sizes and longer duration are needed to evaluate the effectiveness of aflibercept injections in the visual and morphologic improvements following changing previous treatment in persistent DME.

In the current study, we compared a switch group that comprised patients who switched to aflibercept after showing a poor response to previous ranibizumab treatment with a ranibizumab group composed of patients who continued with ranibizumab injections despite the presence of poor response to this treatment. To the best of our knowledge, this is the first study in the literature to compare these treatments in persistent DME.

In conclusion, the results of our study showed that switching therapy from intravitreal ranibizumab to aflibercept in persistent DME provided only morphologic improvement. The discrepancy between morphologic and functional outcomes may be explained by irreversible functional damage caused by long-standing DME.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Treatment Efficacy and Compliance in Patients with Diabetic Macular Edema Treated with Ranibizumab in a Real-Life Setting

Anne-Laurence Best,[1] Franck Fajnkuchen,[1,2] Sylvia Nghiem-Buffet,[1,2] Typhaine Grenet,[1,2] Gabriel Quentel,[2] Corinne Delahaye-Mazza,[2] Salomon Y. Cohen,[2,3] and Audrey Giocanti-Aurégan[1]

[1]*Ophthalmology Department, Avicenne Hospital, DHU Vision and Handicaps, APHP, Paris 13 University, Bobigny, France*
[2]*Centre d'Imagerie et de Laser, Paris, France*
[3]*Ophthalmology Department, Centre Hospitalier Intercommunal de Créteil, Paris Est University, Créteil, France*

Correspondence should be addressed to Audrey Giocanti-Aurégan; audreygiocanti@yahoo.fr

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Purpose. To assess real-life efficacy of ranibizumab and treatment compliance of patients with vision loss secondary to diabetic macular edema (DME). *Methods*. A retrospective study was conducted in DME patients treated with ranibizumab. Patients were monitored every 4 weeks for visual acuity (VA) and central retinal thickness (CRT) by SD-OCT. All patients received a loading dose of 3 monthly injections followed by retreatments on an as-needed basis. The primary endpoint was the change in VA at M12. Patient compliance to the follow-up and the correlation between the injection number and VA were also investigated. Compliance was compared to that of neovascular age-related macular degeneration (nAMD) patients. *Results*. Seventy-two eyes of 55 consecutive DME patients were included. At baseline, the mean VA was 56.5 letters and CRT was 470 μm. At M12, the mean VA was 63.4 letters ($p < 0.0001$), 31.1% of patients had a VA > 70 letters, the mean VA change was +6.9 letters, and the mean CRT was 361.9 μm ($p = 0.0001$) after a mean number of 5.33 intravitreal injections. In patients who received ≥7 injections, the VA gain and final VA were significantly higher than in patients who received <7 injections. At M12, 25.45% of DME patients were lost to follow-up versus 16.8% of nAMD patients ($n = 55$). *Discussion/Conclusion*. Our study confirms the real-life efficacy of ranibizumab in DME at M12 and the need for a large number of injections to achieve better visual outcomes. We also showed a trend to a lower compliance in diabetic versus nAMD patients.

1. Introduction

Diabetic macular edema (DME) is the leading cause of decreased vision in diabetic patients with a prevalence of 4.8% [1]. Its management has improved over the last ten years with the increased availability of therapeutic agents. Laser photocoagulation has long been the reference treatment and has led to a 50% reduction in visual acuity (VA) decrease at 3 years, but this improvement is not sustained over the long term [2]. Thereafter, intravitreal injections (IVI) of corticosteroids have shown promising results [3–6] but their side effects limit their benefits [7, 8]. Ranibizumab was the first anti-VEGF agent to show a benefit in terms of VA in the treatment of central DME [9–12] in Phase III studies. In these pivotal studies, the VA gain over the first year varies from +6.8 to +12 letters with a number of IVI ranging between 7 and 12. The visual gain and IVI number depend on the treatment regimen and follow-up strategies used.

The aim of this study was to assess the efficacy and safety of ranibizumab for the treatment of DME in a real-life setting in a French private practice.

2. Methods

All consecutive patients with vision loss secondary to DME who received their first IVI of ranibizumab 0.5 mg between June 2012 and June 2015 in a private ophthalmology center

specialized in retina diseases, CIL (Center for Imaging and Laser) in Paris, were retrospectively included. This study was conducted in accordance with the tenets of the Declaration of Helsinki, and an informed consent was obtained from patients. Approval was obtained from the France Macula Federation ethics committee.

Inclusion criteria were patients ≥ 18 years old, with type 1 or 2 diabetes with vision loss due to center-involved DME. Both eyes of the same patient could be included.

Exclusion criteria were history of another vitreous or retinal pathology, presence of macular ischemia, stroke or cardiac failure ≤ 3 months before inclusion, and ocular surgery ≤ 6 months before inclusion.

For each patient, the systemic data were collected (diabetes type and duration, HbA1C, blood pressure, dyslipidemia, presence of nephropathy, macroangiopathy, sleep apnea syndrome, and type of treatment).

At baseline and during the follow-up, all patients underwent a complete ophthalmologic examination with best-corrected visual acuity (BCVA) measurement according to the ETDRS scale and slit-lamp and noncontact fundus examination (SuperField Volk). Angiography (Spectralis, Heidelberg Engineering, Heidelberg, Germany) was performed to rule out macular ischemia and to assess the stage of diabetic retinopathy (DR). Spectral-domain optical coherence tomography (SD-OCT) (Spectralis, Heidelberg Engineering, Heidelberg, Germany) was performed to measure the central macular thickness (CRT) and macular volume (MV) during the follow-up. DME was defined by a CRT ≥ 300 μm.

The treatment regimen followed the 2012 European guidelines for ranibizumab use modified in 2014 [13, 14]. Patients received 3 monthly IVI of ranibizumab during the loading phase, followed by reinjection according to a pro re nata (PRN) regimen. Patients were monitored every 4 weeks with BCVA measurement, fundus examination, and CRT measurement. A decrease in BCVA > 5 letters and/or a CRT > 300 μm were indications for retreatment. In the absence of BCVA improvement after the loading phase, treatment was discontinued. Patients with a VA gain < 5 letters or a CRT improvement < 10% from baseline values after 3 IVI were considered as nonresponders.

The primary endpoint was the change in BCVA between baseline and month 12 of follow-up (M12).

Secondary endpoints were the CRT, MV after the loading phase and at M12, number of IVI in the first year of follow-up, and the assessment of patient compliance. Compliance was assessed through 2 parameters: the prevalence of patients lost to follow-up, that is, patients who stopped their follow-up before the end of the first year, and the prevalence of patients with an irregular follow-up, that is, patients who did not attend the required appointments and missed their examination between M12 and M14, but continued their treatment. The compliance of DME patients was compared to that of a series of consecutive neovascular age-related macular degeneration (nAMD) patients treated with ranibizumab for one year in the same center, during the same period.

2.1. Statistical Analysis. A matched Student parametric test was used for statistical analysis, and a p value < 0.05 was considered significant. For prevalence comparison, a Fisher's exact test was performed. The statistical analysis was carried out using Prism 7 software.

3. Results

Seventy-two eyes of 55 patients treated with ranibizumab injections were included. Seventeen patients (30.9%) had bilateral DME, and 38 patients (69.1%) had unilateral DME. The mean DME duration before the first injection was 20.2 months.

The mean follow-up duration after the first IVI was 19.6 months (±11.39 months), with a median of 17.87 months. Baseline patient characteristics are presented in Table 1.

Diabetic retinopathy (DR) was mild nonproliferative DR (NPDR) in 5 eyes (7%), moderate NPDR in 18 eyes (25%), severe NPDR in 20 eyes (27.8%), and proliferative DR in 8 eyes (11.1%). Laser photocoagulation had been previously performed in 21 eyes (29.1%).

Twenty-seven eyes (37.5%) were not treatment naive: 26 eyes had received macular laser therapy and 1 eye had been treated with IVI of triamcinolone in 2004 prior to inclusion. Forty-five eyes (62.5%) were treatment naive (Table 2).

3.1. Functional Outcomes. The mean baseline BCVA was 56.5 ± 11.9 ETDRS (±SD) letters. Five out of the 72 (6.9%) eyes had a baseline BCVA score > 70 ETDRS (Table 3, Figure 1).

The mean BCVA gain was +6.4 ± 7.3 letters at M3 ($p < 0.0001$), +6.1 ± 16.7 letters at M6 ($p < 0.0001$), +6.5 ± 8.5 letters at M9 ($p < 0.0001$), and +6.9 ± 10.2 ETDRS letters at M12 ($p < 0.0001$). After one year of treatment, 37.8% (17/45) of patients had a VA gain ≥ 10 letters and 22.2% (10/45) had ≥15 letters and 31.1% (14/45) had reached the BCVA threshold of >70 letters versus only 6.9% at baseline.

At the end of the first year of follow-up, 2 eyes had lost ≥10 letters.

3.2. Anatomical Outcomes. The mean baseline CRT was 470 μm (±134.5). The mean CRT change was −148 μm (±177) at M3 and −108.1 μm (±176) at M12 (Table 3, Figure 2). CRT was <300 μm in 40% (18/45) of eyes at M12.

The baseline MV was 13.2 mm^3. The mean change in MV was −2 ± 1.6 mm^3 at M3 and −1.6 ± 1.6 mm^3 at M12 (Table 3, Figure 3).

3.3. Number of Intravitreal Injections. 55 patients (72 eyes) received a mean number of 5.33 ± 2.1 injections of ranibizumab over the first year. Nineteen eyes had a follow-up of two years with a mean number of 10.84 IVI.

3.4. Compliance with Treatment. Nine (16.4%) and 14 (25.45%) patients (10 and 16 eyes) were lost to follow-up at M6 and M12, respectively. As a result, 41 patients (56 eyes) had at least 12 months of follow-up, but only 33 out of the 55 patients (60%, 45 eyes) attended the control consultation scheduled between the 12th and 14th month, the others were seen later (i.e., 8 patients—14.5%—had an irregular follow-up).

Table 1: Baseline characteristics of patients.

Patient number	$n = 55$
Sex	
Men	$n = 34$ (61.8%)
Women	$n = 21$ (38.2%)
Type of diabetes	
Type 1	$n = 8$ (15.5%)
Type 2	$n = 47$ (85.5%)
Age (years), mean (±SD*)	66.7 (±9.59)
Duration of diabetes (years), mean (±SD)	18.1 (±13.29)
HbA1c, mean (±SD)	7.4% (±1.25)
Insulinotherapy	$n = 20$ (36%)
High blood pressure	$n = 34$ (61.8%)
Dyslipidemia	$n = 14$ (25%)
Nephropathy	$n = 15$ (27%)
Macroangiopathy	$n = 2$ (3.6%)
Sleep apnea syndrome	$n = 2$ (3.6%)

*SD: standard deviation.

Table 2: Baseline features of retinopathy, maculopathy, and ophthalmologic history.

Eye number	$n = 72$
NPDR	
Mild	5 (7%)
Moderate	18 (25%)
Severe	20 (27.7%)
PDR	8 (11.1%)
Laser photocoagulation	
PRP	
Ongoing	22 (30.5%)
Completed	21 (29.1%)
Focal/grid	26 (36.1%)
Intravitreal injection history	
Corticosteroids	1 (1.3%)
DME duration (months): mean (±SD)	20.2 (±25.13)
Pseudophakic	18 (25%)
Vitreomacular surgery	4 (5.6%)
Epiretinal membrane	10 (13.8%)
High intraocular pressure history	4 (5.5%)

NPRD: nonproliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; PRP: panretinal photocoagulation; SD: standard deviation; *n*: number of eyes.

3.5. Baseline Characteristics and Compliance of nAMD Patients. Fifty-five consecutive patients with nAMD seen in the same private practice and requiring ranibizumab IVI since January 2013 and followed over 12 months were also included. We included 41 women and 14 men with a mean age of 85.3 (±6.3). The mean baseline visual acuity was 61.6 (±13.5) letters.

A mean number of 7.38 consultations were carried out over one year. A mean number of 4.5 IVI were administered over the first year. Only 16.8% of patients were lost to follow-up at one year.

3.6. Subgroup Analysis

3.6.1. Subanalysis according to the Number of IVI at 1 Year. Two subgroups of patients were defined based on the number of IVI administered during the first year: one group received <7 IVI ($n = 30$ eyes) and one received ≥7 IVI ($n = 15$ eyes). Patients who received <7 IVT had a baseline BCVA of 55.5 letters and a visual gain of +5.43 letters versus a baseline BCVA of 57.1 letters ($p = 0.09$) and a visual gain of +11.19 letters for patients who received ≥7 IVT. At one year, a mean BCVA of 60.96 ± 15.66 letters was achieved in the group that received <7 IVT versus 68.26 ± 6.99 letters in the group with ≥7 IVT ($p = 0.04$).

3.6.2. Functional Response Subanalysis at 1 Year. Two subgroups were defined according to the functional response after one year of treatment. A subgroup of good responders ($n = 8$ eyes) was defined as a BCVA gain > 15 letters at 1 year, and a subgroup of poorer responders was defined by a BCVA gain ≤ 15 letters. The group of poorer responders received fewer IVI than the group of good responders (mean IVI number: 5.59 versus 6.5) over the first year ($p = 0.03$). In the good responder group, the baseline BCVA was 46.9 letters and 58.2 letters in the poorer responders ($p = 0.047$).

3.7. Safety. No case of endophthalmitis was reported during the follow-up. One patient with type 2 diabetes had a stroke 6 weeks after the last IVI. This patient subsequently underwent a complete ophthalmologic evaluation, and the decision was made to discontinue IVI.

4. Discussion

The results of our study confirm the efficacy of ranibizumab for the treatment of DME responsible for vision loss in a real-life setting with a VA gain of $+6.9 \pm 10.2$ letters after a mean number of 5.33 IVT over the first year of follow-up.

However, our functional results at 1 year are slightly lower than those reported in pivotal [10] and http://drcr.net studies [8, 12, 15] which show a gain from +6.5 to +12 letters at M12. This discrepancy could probably be due to an insufficient number of injections in our real-life series. Indeed, in our study, patients received 5.33 IVI with a mean annual number of 7.68 consultations, compared to 7–9.4 IVI in pivotal and DRCR.net studies with a number of consultations generally higher than that of our patients.

In the RISE and RIDE studies [11], patients were injected monthly for 36 months. In this case, the VA gains ranged from +11.9 to +12 letters [16] after one year of follow-up. In Europe, in the RESTORE study [10], with a strict monthly monitoring, the visual gain was +6.8 letters at the end of the first year of treatment with a mean number of 7 IVI. Patients were treated according to a PRN regimen, and the retreatment criterion was strictly functional.

Table 3: Best-corrected visual acuity (BCVA), central retinal thickness (CRT), and macular volume (MV) over the first year of follow-up.

	Baseline	Month 3	Month 6	Month 9	Month 12
Number of eyes	$n = 72$	$n = 60$	$n = 58$	$n = 52$	$n = 45$
BCVA (ETDRS letters ± SD)	56.5 ± 11.9	62.9 ± 12.4	62.6 ± 13.0	63.0 ± 12.2	63.4 ± 13.8
CRT (μm ± SD)	470 ± 134.5	322 ± 97.8	344.7 ± 122.8	350.5 ± 99	361.9 ± 124.8
MV (mm^3 ± SD)	13.2 ± 2.4	11.2 ± 1.5	11.4 ± 1.7	11.6 ± 1.7	11.6 ± 1.6
BCVA > 70 letters	5 (6.9%)	22 (36.6%)	18 (31%)	16 (30.7%)	14 (31.1%)
		0–3 months	0–6 months	0–9 months	0–12 months
Number of eyes	$n = 72$	$n = 60$	$n = 58$	$n = 52$	$n = 45$
BCVA gain (ETDRS letters ± SD)		+6.4 ± 7.3*	+6.1 ± 16.7*	+6.5 ± 8.5*	+6.9 ± 10.2*
Change in CRT (μm ± SD)		−148 ± 177	−125.3 ± 177	−119.5 ± 143	−108.1 ± 176
Change in MV (mm^3 ± SD)		−2 ± 1.6	−1.8 ± 1.8	−1.7 ± 1.4	−1.6 ± 1.6
Gain ≥ 10 letters		22 (30.5%)	19 (26.3%)	18 (25%)	17 (37.8%)
Gain ≥ 15 letters		9 (12.5%)	11 (15.2%)	5 (6.9%)	10 (22.2%)
Loss ≥ 10 letters		1 (1.3%)	6 (8.3%)	2 (2.7%)	3 (4.1%)
Loss ≥ 15 letters		0	3 (4.1%)	0	2 (2.7%)

*$p < 0.0001$.

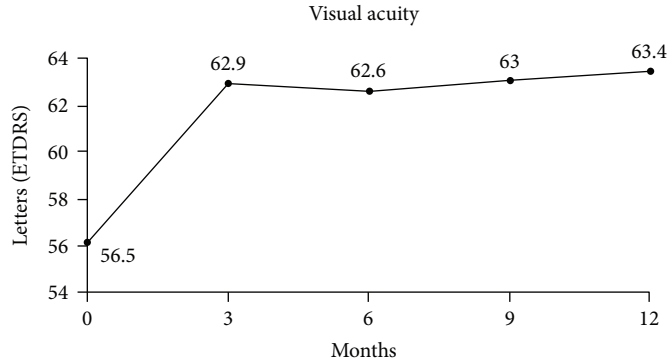

Figure 1: Mean change in best-corrected visual acuity over the first year of follow-up.

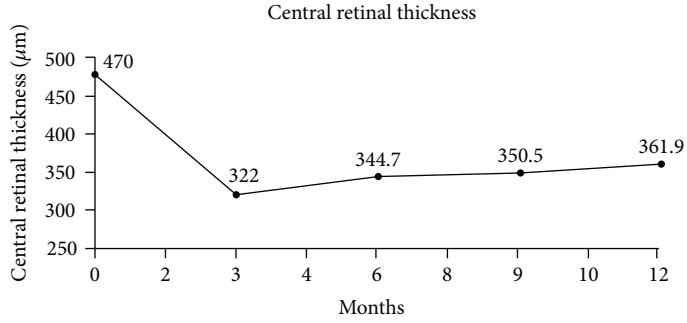

Figure 2: Mean change in central retinal thickness over the first year of follow-up.

In the DRCR.net studies [8, 12, 15], ranibizumab IVI were administrated according to a PRN regimen with retreatment based on functional and anatomical outcomes with severe retreatment criteria during the first 6 months to achieve a VA of 20/20 or a dry retina. Thus, patients usually received 5 or 6 injections during the first 24 weeks. With this type of treatment and monitoring every 4 weeks, a gain of +9 letters after 9 IVI was observed with protocol I and +11.2 letters after 10 IVI with protocol T. However, in our study, despite consultations scheduled every 4 weeks, the time between each consultation was longer than 4 weeks in patients who completed the one-year follow-up since they only attended a mean number of 7.68 visits over 12 months.

A clear difference in terms of visual outcomes between the real-life setting and pivotal studies has already been observed in nAMD patients treated with ranibizumab. In

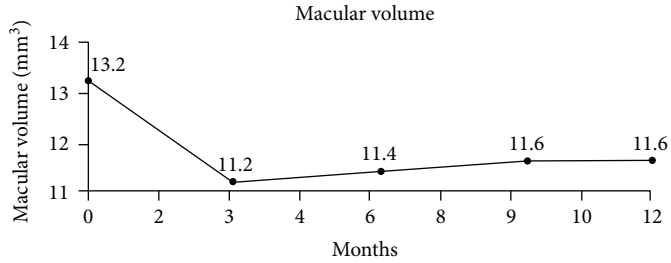

Figure 3: Mean change in macular volume over the first year of follow-up.

nAMD, the MARINA [17] and ANCHOR [18] pivotal studies have shown VA gains ranging between +7.2 and +11.3 letters at one year. The PrONTO study [19] has shown a sustained VA improvement with a personalized PRN regimen and retreatment based on functional and anatomical outcomes allowing a gain of +9.3 letters at one year with twice fewer injections but with a proper monthly follow-up. Real-life studies have shown a smaller improvement with a gain of +4.4 letters at one year for the LUMINOUS [20] study. Another real-life study conducted in our center has shown an even lower visual gain of +0.7 letter after 3.79 IVI and 8.06 consultations over the first year under a PRN regimen, and the authors have concluded on the need for a more regular follow-up with a strict 4-week interval between each consultation. These real-life studies have stressed that there could be a difference in terms of functional outcomes between data from randomized studies with a strict monitoring and treatment protocols and the real-life conditions.

In DME, differences in functional outcomes seem less significant than in nAMD between pivotal and real-life results. The ADMOR real-life study [21] has investigated the efficacy of ranibizumab in patients with DME in South Asia. The results showed a gain of +8.5 letters at 1 year with a mean number of 7 ± 2 IVI over the first year. In this study, patients were not strictly monitored every 4 weeks and attended a mean number of 10 ± 2 visits during their follow-up. Patients in the ADMOR study had a more severe DME, with an initial VA less than ours (55.3 ± 13.4 letters), and a higher baseline CRT (532 ± 129 μm). Another real-life study by Hrarat et al. [22] has reported a gain of +10.7 $\pm$ 16.9 letters after 12 months of treatment with a mean number of 5.4 ± 1.9 IVI and 8.8 ± 2.5 visits during the follow-up. The mean baseline VA was 48.3 ± 17 letters, and the baseline CRT was 519.7 ± 157.3 μm. This very low baseline VA could explain their high VA gain [16]. A Swedish real-life study by Granström et al. [23] assessing the efficacy of a 12-month treatment with ranibizumab in DME, retrospectively conducted in two ophthalmic departments using a PRN regimen, has reported a gain of +5.2 letters after 12 months of treatment, but the mean number of injections was not specified. Patients had an initial VA greater than ours (65.0 ± 12.1 letters) with a lower initial CRT: 403 ± 122 μm.

In our study, with a stricter follow-up and treatment regimen, the VA gains could have probably been greater. This finding is reinforced by a statistically significant correlation between the VA gain and the number of IVI in our study. Patients with more than 7 IVI had a higher VA gain than those who received less than 7 IVI ($p < 0.04$). In addition, the number of injections was greater in the group of patients who had a gain greater than 15 letters compared to the group that did not exceed this threshold ($p < 0.03$).

These results encourage us to adopt a strict follow-up and highlight the need for a regular follow-up by providing appropriate information to patients. Appropriate information is indeed important as the compliance of diabetic patients may be low. Thus, in our series, it should be noted that a significant number of patients were lost to follow-up (25.45% of patients), suggesting that some diabetic patients are poorly compliant. The small percentage of patients (60%) who attended the 12-month consultation supports this hypothesis. This discrepancy between real-life and pivotal studies stresses that real-life studies are necessary to assess the true efficacy of a treatment and to understand the factors limiting efficacy.

The treatment regimen of DME represents a real burden for patients and their family, and diabetic patients must also attend different medical consultations with several specialists and this may be a barrier to a monthly follow-up. Thus, this burden of consultations not only with ophthalmologists could contribute to the lower compliance of diabetic patients compared to that of nAMD patients. Indeed, we assessed in the same private practice 55 consecutive patients with nAMD requiring ranibizumab IVI and followed them over 12 months. They attended a mean number of 7.38 consultations and received a mean number of 4.5 IVI over the first year. Only 16.8% of patients were lost to follow-up at one year versus 25.45% in our series of diabetic patients ($p = 0.6$).

Different assumptions may be made regarding the lower compliance of diabetic patients compared to AMD patients: the fact that (i) DME is part of a chronic extraophthalmological disease, diabetes, which, because of its chronicity, may lead to a lassitude with regard to the disease; (ii) the loss of vision is progressive in DME compared to the sudden and often deeper vision loss in nAMD; (iii) diabetic patients are younger and often in the working age, making them less available than nAMD patients who are often retired; and (iv) the cost of the treatment, which may also be a barrier, in particular in a private center where patients must advance the cost. Other studies are needed to confirm the lower compliance of DME patients compared to nAMD patients.

Based on our findings and the results of the literature [24], it seems essential to adopt the treatment regimen to specificities of the diabetic population and to patient availability and preferences after information and, in the case of

patients who cannot follow a strict monthly regimen to choose the appropriate treatment, for instance, a treat-and-extend regimen, providing the same visual outcomes with a lower number of consultations [24] and thus, even despite a possible overtreatment for a few patients.

In conclusion, our real-life study shows a VA improvement in patients with DME, with however a slightly lower gain than that found in pivotal studies after a lower number of IVI. This discrepancy between results obtained in a real-life setting and pivotal studies is not as important as in nAMD despite a higher compliance of nAMD patients in a real-life setting.

This study also shows that the visual outcomes correlate with the number of IVI, and that a strict monthly follow-up is challenging in the real life.

Disclosure

This study was presented as a paper at the French Society of Ophthalmology in Paris by May 2016 and as a poster at ARVO Meeting in Seattle by May 2016.

Conflicts of Interest

Dr. Audrey Giocanti-Aurégan reports personal fees from Allergan, Alimera, Bayer, Novartis, and Optos plc outside the submitted work. Dr. Franck Fajnkuchen and Dr. Typhaine Grenet report personal fees from Allergan, Bayer, and Novartis outside the submitted work. Dr. Sylvia Nghiem-Buffet reports personal fees from Allergan, Bayer, Novartis, and Zeiss outside the submitted work. Dr. Corinne Delahaye-Mazza and Dr. Anne-Laurence Best have nothing to disclose. Dr. Gabriel Quentel reports personal fees from Novartis outside the submitted work. Professor Salomon Y. Cohen reports personal fees from Novartis, Bayer, Allergan, Alcon, and Thea outside the submitted work.

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