Targeted Retinal Photocoagulation for Diabetic Macular Edema with Peripheral Retinal Nonperfusion

Purpose

To evaluate the effect of targeted retinal photocoagulation (TRP) on visual and anatomic outcomes and treatment burden in eyes with diabetic macular edema (DME).

Design

Phase I/II prospective, randomized, controlled clinical trial.

Participants

Forty eyes of 29 patients with center-involved macular edema secondary to diabetes mellitus.

Methods

Eyes with center-involved DME and Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) between 20/32 and 20/320 (Snellen equivalent) were randomized 1:1 to monotherapy with 0.3 mg ranibizumab (Lucentis, Genentech, South San Francisco, CA) or combination therapy with 0.3 mg ranibizumab and TRP guided by widefield fluorescein angiography. All eyes received 4 monthly ranibizumab injections followed by monthly examinations and pro re nata (PRN) re-treatment through 36 months. Targeted retinal photocoagulation was administered outside the macula to areas of retinal capillary nonperfusion plus a 1–disc area margin in the combination therapy arm at week 1, with re-treatment at months 6, 18, and 25, if indicated.

Main Outcome Measures

Mean change in ETDRS BCVA from baseline and number of intravitreal injections administered.

Results

At baseline, mean age was 55 years, mean BCVA was 20/63 (Snellen equivalent), and mean central retinal subfield thickness (CRT) was 530 µm. Thirty-four eyes (85%) completed month 36, at which point mean BCVA improved 13.9 and 8.2 letters ($P = 0.20$) and mean CRT improved 302 and 152 µm ($P = 0.03$) in the monotherapy and combination therapy arms, respectively. The mean number of injections administered through month 36 was 24.4 (range, 10–34) and 27.1 (range, 12–36), with 73% (362/496) and 80% (433/538) of PRN injections administered ($P = 0.004$) in the monotherapy and combination therapy arms, respectively. Goldmann visual field isopter III-4e area decreased by 2% and 18% in the monotherapy and combination therapy arms, respectively ($P = 0.30$).

Conclusions

In this 3-year randomized trial of 40 eyes with DME, there was no evidence that combination therapy with ranibizumab and TRP improved visual outcomes or reduced treatment burden compared with ranibizumab alone.

Abbreviations and Acronyms:

BCVA (best-corrected visual acuity), CRT (central retinal subfield thickness), DAVE (Efficacy and Safety Trial of Intravitreal Injections Combined with Panretinal Photocoagulation for Clinically Significant Macular Edema Secondary to Diabetes Mellitus), DME (diabetic macular edema), ETDRS (Early Treatment Diabetic Retinopathy Study), FA (fluorescein angiography), GVF (Goldmann visual field), PDR (proliferative diabetic retinopathy), PRN (pro re nata), PRP (panretinal photocoagulation), SD (spectral-domain), TRP (targeted retinal

photocoagulation), VEGF (vascular endothelial growth factor A)
Chronic hyperglycemia in diabetes mellitus leads to microvascular damage throughout the body, and the retinal capillary beds often are the first and most severely affected of end organs. Shimizu et al demonstrated in 1980 that the mid-peripheral retinal vasculature was affected profoundly, with marked nonperfusion demonstrated on a montage of fundus fluorescein angiography (FA) images that correlated with diabetic retinopathy levels of increasing severity. This nonperfused hypoxic retina and the surrounding penumbra of underperfused retina is now known to upregulate the hypoxia-inducible factor transcriptional cascade, leading to secretion of a multitude of vasoactive cytokines, including vascular endothelial growth factor A (VEGF) and erythropoietin, which lead to both proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME). Although panretinal photocoagulation (PRP) to the mid-peripheral and peripheral retina have been the mainstay for treatment of proliferative disease since the Diabetic Retinopathy Study, PRP in the Early Treatment Diabetic Retinopathy Study (ETDRS) seemed to have adverse effects on vision in the short term, with these effects more pronounced with full scatter than with mild scatter. Indeed, PRP in the era before anti-VEGF therapy more typically was associated with increased DME.

In the management of DME, long-term suppression of VEGF reduces DME and improves visual acuity, but most patients require repeated, ongoing anti-VEGF injections for optimal outcomes. To decrease VEGF production, numerous authors have proposed PRP to the mid-peripheral and peripheral retina, and several case series and small, brief studies have implied that targeted retinal photocoagulation (TRP) guided by widefield FA can decrease treatment burden (i.e., decrease the need for ongoing anti-VEGF injections). Based on these studies and the widespread belief that substantial VEGF production emanates from the involved nonperfused or adjacent retina, many clinicians advocate peripheral PRP or TRP to nonperfused retina in the setting of DME. To test the hypothesis that widefield FA–guided TRP significantly reduces the number of required anti-VEGF injections, the Efficacy and Safety Trial of

Intravitreal Injections Combined with Panretinal Photocoagulation for Clinically Significant Macular Edema Secondary to Diabetes Mellitus (DAVE) was designed to assess the long-term (3-year) effects of combination therapy with ranibizumab injections versus ranibizumab injections alone on visual acuity, anatomic features, and reduction in demand for anti-VEGF therapy.

Methods

The DAVE trial was a phase I/II randomized clinical trial (clinicaltrials.gov identifier, NCT01552408; Food and Drug Administration Investigational New Drug identifier, 113691). Institutional review board/ethics committee approval (Sterling IRB, Atlanta, GA) was obtained for this Health Insurance Portability and Accountability Act–compliant trial that adhered to the tenets of the Declaration of Helsinki. Data were collected at the Retina Consultants of Houston (Houston, Katy, and Woodlands, Texas). Patients older than 18 years with center-involving macular edema secondary to either type 1 or 2 diabetes mellitus, ETDRS best-corrected visual acuity (BCVA) between 24 and 78 letters (Snellen equivalent, 20/320 and 20/32, respectively), and central retinal subfield thickness (CRT) of 250 μm or more as measured by spectral-domain (SD) OCT were eligible for inclusion. All eyes had severe nonproliferative diabetic retinopathy or early PDR. According to the protocol, eyes with high-risk PDR defined by the Diabetic Retinopathy Study criteria were excluded. Only eyes with distinct and extensive areas of capillary nonperfusion outside the vascular arcades on widefield FA (OPTOS 200Tx; Optos, Dunfermline, United Kingdom) that the evaluating investigator believed would benefit from TRP were eligible for enrollment and randomization. The baseline retinal nonperfusion in square millimeters was graded by the Doheny Reading Center. At enrollment, patients were randomized 1:1 to either monotherapy or combination therapy arms and written, informed consent was obtained. For patients who had both eyes enrolled (n = 11), each eye was assigned to a different arm. Pertinent exclusion criteria included any history of PRP, vitrectomy, or other eye conditions that could alter BCVA. A list of major inclusion and exclusion criteria is presented in Table 1.

Table 1Key Inclusion and Exclusion Criteria

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study.

At all visits, participants underwent ETDRS BCVA testing, slit-lamp and dilated ophthalmic examination, and SD OCT using the Heidelberg Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany). The Heidelberg SD OCT acquisition protocol used volume-per-cube (20 × 20, 49 lines, 768 A-scans per line) with 9-times image averaging. Color fundus photography and widefield FA (200°) were conducted at baseline and repeated every 3 months using the Optos 200Tx. Goldmann visual field (GVF) testing was conducted at baseline and was repeated every 6 months.

All participants received 0.05-ml intravitreal injections of 0.3-mg ranibizumab administered monthly (28±7 days) for 4 treatments starting at baseline. Patients randomized to the combination therapy arm underwent TRP at week 1 with possible re-treatment at months 6, 18, and 25 based on repeat widefield FA results. Peripheral, targeted laser was administered after topical, subconjunctival, or retrobulbar anesthesia, directed to areas of nonperfused peripheral retina plus a 1–disc area margin (Fig 1). At the initial laser treatment, no less than 800 and no more than 2400 applications were applied; at subsequent treatments, the extent of laser was determined by the treating investigator based on areas of nonperfusion identified by widefield FA. Laser was applied with both slit-lamp and indirect laser to achieve consistent coverage to the ora serrata. Afterward, all patients were evaluated monthly and treated on a pro re nata (PRN) basis with re-treatment determined based on the presence of center-involving DME through the end of the trial, month 36. Specifically, ranibizumab injections were administered if DME was demonstrated by SD OCT to involve the foveal depression. The decision for re-treatment was performed in a masked fashion to avoid bias in determining the need for re-treatment.

Figure 1Representative widefield fluorescein angiography (FA) images of targeted retinal photocoagulation

(TRP) applied to nonperfused peripheral retina in the combination therapy arm. **A**, Baseline widefield FA image demonstrating extensive nonperfusion. **B**, Month 6 widefield FA image demonstrating TRP and shoulder zones of residual nonperfusion that then were targeted with additional TRP (*red circles*). **C**, Month 27 widefield FA image showing heavy TRP applied peripherally with sparing of macula.

Sterile technique was followed for every intravitreal injection. Topical anesthetic was instilled and the use of subconjunctival anesthesia was optional at the investigator's discretion (2% lidocaine without epinephrine at the injection site). After topical anesthesia, 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. After intravitreal injection, finger-counting testing was performed to confirm central retina artery perfusion, and intraocular pressure was measured 30 minutes (±10 minutes) after injection. Participants were monitored until intraocular pressure measured 30 mmHg or less. Peri-intravitreal injection topical ophthalmic antibiotics were not used.

The primary outcome measures at month 36 included mean change in ETDRS BCVA from baseline and number of intravitreal injections administered. Secondary outcome measures included percentage of patients gaining or losing 15 ETDRS letters or more from baseline, mean change in CRT, mean change in peripheral visual field as measured by GVF testing, and incidence and severity of adverse events. The last observation carried forward method was used to impute data for patients who did not complete month 36, but who completed at least the first year of the trial.

Accuracy of SD OCT automated segmentation (internal limiting membrane and Bruch's membrane) was evaluated and segmentation errors were corrected manually before computation of change in CRT. Eyes completing GVF testing at baseline and month 36 with adequate fixation and cooperation during testing were included in GVF analyses (n = 17). Goldmann visual field area of field (III-4e isopter) was calculated after transferring to Adobe Photoshop CC (Adobe Systems, San Jose, CA) by the method published by Zahid et al. The paired and unequal-variances *t* tests were used to compare continuous variables, and the chi-square test or Fisher exact test were used to compare categorical variables, as appropriate. Treatment group differences in BCVA and CRT outcomes at month 36 also were analyzed by analysis of covariance with baseline values as covariates. Using a standard deviation of 5 injections as reported for the ranibizumab arm of the Diabetic Retinopathy Clinical Research Network protocol T, the study had 79% power to detect a mean difference of 4.5 injections using the Student *t* test. Statistical comparisons were performed using R software version 3.3.1 (R Project for Statistical Computing, Vienna, Austria; www.r-project.org).

Results

Forty eyes of 29 patients were enrolled between May 2012 and August 2014. Baseline demographics were relatively balanced between eyes randomized to the monotherapy (n = 20) and combination therapy (n = 20) arms (Table 2). At baseline, mean age was 55 years (range, 31–75 years) and mean glycated hemoglobin was 8.6% (range, 5.9%–12.9%). Of the patients, 24% (7/29) were women. Baseline mean BCVA was 59.1 ETDRS letters (Snellen equivalent, 20/63) and 60.1 ETDRS letters (Snellen equivalent, 20/63) in the monotherapy and combination therapy arms, respectively. The mean baseline nonperfusion area of the entire study population was 196.1±123.4 mm^2. There was no difference in mean nonperfusion area between the monotherapy group (195.63±150.67 mm^2) and the combination cohort (198.25±101.65 mm^2; $P = 0.995$). Baseline mean CRT was thinner in the combination therapy arm: 488 versus 571 µm ($P = 0.17$). Thirty-four eyes (85%) of 24 patients (83%) completed month 36. Six patients withdrew consent at months 1, 1, 5, 18, 34, and 34 because of loss to follow-up, relocation, or personal choice. Of 1437 scheduled visits through month 36, 141 (10%) were missed.

Table 2Baseline Patient Demographics

BCVA = best-corrected visual acuity; CRT = central retinal subfield thickness; DM = diabetes mellitus; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA1c = glycated hemoglobin; SD = standard deviation.

Visual Acuity Outcomes

Visual acuity increased in both arms from baseline through month 36 (Fig 2). At month 4, after 4 mandatory monthly loading doses, the mean ± standard deviation changes in ETDRS BCVA were 7.9±8.1 and 8.0±7.5 letters in the monotherapy and combination therapy arms, respectively, compared with baseline (*P* = 0.96). At month 12, the mean ± standard deviation change in ETDRS BCVA was 15.7±11.3 letters in the monotherapy arm and 9.8±8.8 letters in the combination therapy arm compared with baseline. At month 24, the mean ± standard deviation change in ETDRS BCVA was 16.1±9.4 letters in the monotherapy arm and 8.6±14.1 letters in the combination therapy arm compared with baseline. At month 36, the mean ± standard deviation change in ETDRS BCVA was 13.9±10.2 letters in the monotherapy arm (n = 18) and 8.2±16.1 letters in the combination therapy arm (n = 19; *P* = 0.20), resulting in absolute mean BCVA of 71.6 and 68.2 letters, respectively (*P* = 0.45). An analysis of covariance model for month 36 visual outcomes including baseline letter score as a covariate found a treatment effect of 4.6 letters in favor of monotherapy, although this was not statistically significant (*P* = 0.26). Of eyes that were evaluated at month 36, 12 (67%) and 9 (47%) gained 10 letters or more (*P* = 0.24) and 9 (50%) and 5 (26%) gained 15 letters or more (*P* = 0.14) in the monotherapy (n = 18) and combination therapy (n = 19) arms, respectively (Table 3). One eye in the combination therapy arm lost 36 letters at month 36 because of persistent DME and foveal capillary dropout despite monthly treatment. No other patient in either arm lost more than 10 letters. A subanalysis of the 11 patients who had both eyes enrolled (n = 22 eyes) revealed mean ± standard deviation month 36 BCVA gains of 13.6±10.1 and 7.5±19.5 letters for the monotherapy and combination therapy arms, respectively (*P* = 0.40).

Figure 2Graph showing mean Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) through month 36.

Table 3Distribution of Vision Changes

At baseline, mean Goldmann III-4e isopter area was 10 291 degrees^2 in the monotherapy (n = 9) arm and 9826 degrees^2 in the combination therapy (n = 8) arm (P = 0.73). By month 36, III-4e isopter area declined by 216 degrees^2 (2%) and 1724 degrees^2 (18%) in the monotherapy and combination therapy arms, respectively (P = 0.30), to absolute mean isopter areas of 10 076 and 8102 degrees^2, respectively.

Anatomic and Treatment Burden Outcomes

Through month 36, mean CRT decreased in both arms (Fig 3). Mean ± standard deviation CRT changes at month 12 were −301±255 and −161±188 μm in the monotherapy and combination therapy arms, respectively. Mean ± standard deviation CRT changes at month 24 were −296±238 and −169±172 μm in the monotherapy and combination therapy arms, respectively. Mean ± standard deviation CRT changes at month 36 were −302±246 and −152±149 μm in the monotherapy and combination therapy arms, respectively (P = 0.03), yielding an absolute mean CRT of 286 and 344 μm (P = 0.09). When CRT outcomes were modeled with baseline CRT as a covariate, no significant treatment effect was identified (P = 0.07), with an estimate of 64 μm in favor of monotherapy. Among eyes evaluated at month 36, 14 (76%) and 9 (47%) had CRT less than 320 μm (P = 0.057) in the monotherapy (n = 18) and combination therapy (n = 19) arms, respectively. A subanalysis of the 11 patients who had both eyes enrolled (n = 22 eyes) revealed mean ± standard deviation month 36 CRT changes of −300±264 and −166±144 μm for the monotherapy and combination therapy arms, respectively (P = 0.03).

Figure 3Graph showing mean central retinal thickness through month 36.

Among eyes that completed month 36, a mean of 24.4 ranibizumab injections (range, 10–34 injections) were administered in the monotherapy arm and a mean of 27.1 ranibizumab injections (range, 12–36 injections) were administered in the combination therapy arm (Fig 4). Through month 36, 73% (362/496) of possible PRN injections were administered in the monotherapy arm and 80% (433/538) of possible PRN injections were administered in the combination therapy arm ($P = 0.004$). When data were stratified by year, injection frequency was significantly different between arms in the second year (monotherapy, 72% [137/190]; combination therapy, 81% [161/198]; $P = 0.03$), but not in the first year (monotherapy, 86% [126/146]; combination therapy, 90% [141/156]; $P = 0.27$) or in the third year (monotherapy, 62% [99/160]; combination therapy, 71% [131/184]; $P = 0.07$). A subanalysis of the 11 patients who had both eyes enrolled (n = 22 eyes) revealed 24.2 and 27.2 mean injections given through month 36 in the monotherapy and combination therapy arms, respectively, with 74% (227/307) and 83% (256/309) of PRN injections administered ($P = 0.007$). Sixteen eyes (80%) in the combination therapy cohort underwent a mean of 1.5 additional TRP sessions after the initial session at baseline.

Figure 4Bar graph showing the distribution of the total number of injections administered through month 36 in the monotherapy and combination therapy arms.

Adverse Events

Ocular adverse events and serious adverse events are reported in Table 4. Two eyes, both in the monotherapy arm, demonstrated neovascularization of the iris with neovascular glaucoma requiring surgical treatment. One of these neovascular glaucoma eyes also demonstrated neovascularization of the disc and of the mid periphery. Three additional eyes in the monotherapy arm demonstrated posterior neovascularization (neovascularization of the mid periphery, neovascularization of the disc, or both). One eye in the combination therapy arm experienced acute vision loss secondary to a vitreous hemorrhage without fluorescein evidence of posterior neovascularization. In total, 5 eyes in the monotherapy arm demonstrated new PDR-associated neovascularization compared with none in the combination therapy arm. There were no instances of endophthalmitis.

Table 4Adverse Events

Data are no. (%).

∗ Systemic events experienced by patients with both eyes enrolled are reported in both columns. Events are reported on a per-patient basis.

Discussion

In 1983, Shimizu et al commented, “Panretinal photocoagulation brings about a dramatic improvement in the macula even though the latter is not directly treated by photocoagulation,” and in 1991, Gardner et al reported reduction of severe macular edema after PRP for PDR in 13 of 18 diabetic eyes with poor vision. The availability of widefield FA now allows consistent 200° retinal imaging, making it much easier to assess capillary nonperfusion in the mid-peripheral and far-peripheral retina in retinal vascular diseases. Wessel et al used widefield FA to demonstrate that eyes with peripheral retinal nonperfusion had 3.75-times increased odds of having DME compared with eyes without retinal nonperfusion ($P <$ 0.02).

Based on the availability of widefield FA, many reports have described targeted retinal photocoagulation to mitigate loss of useful visual field for the treatment of PDR and ischemic retinal vein occlusion. Essentially, widefield FA is used to delineate areas of retina that appear to be nonperfused, and generally surgeons target these areas and the hyperfluorescent surrounding penumbra with tight patterns of laser photocoagulation. Two brief trials with 6-month follow-up reported the use of widefield FA–targeted laser in combination with anti-VEGF treatments and suggested that this combination reduced the treatment burden with fewer required anti-VEGF injections. Neither study examined the effect of widefield FA–targeted laser to nonperfusion as an independent variable with other factors remaining constant. The RaScaL trial studied eyes with combination therapy of ranibizumab plus widefield FA–guided laser compared with a control group that received combination therapy of intravitreal triamcinolone plus traditional focal laser. Takamura et al compared focal laser plus bevacizumab with focal laser plus bevacizumab plus targeted laser in a group of patients in which two thirds of eyes already had received traditional PRP. Because numerous studies have identified that anti-VEGF therapy for DME often needs fewer

injections over several years of therapy,' ' the DAVE trial was designed to isolate the effects of dense targeted photocoagulation to widefield FA–identified areas of capillary nonperfusion as a single independent variable over a 36-month trial. Only eyes with no prior PRP were included, and ranibizumab re-treatment criteria were identical in both the control and experimental arms (4 loading doses and then 32 monthly examinations with a predefined PRN ranibizumab injections protocol when DME disturbed the foveal depression on SD OCT examination).
The main goal of TRP in the DAVE trial was to decrease VEGF production theoretically to decrease the number of PRN ranibizumab injections required to control DME affecting the fovea. Only eyes with extensive capillary nonperfusion were enrolled, and all areas of nonperfusion as well as the margin of perfused retina were treated with heavy photocoagulation (Fig 1). This included indirect laser to the ora serrata in the combination therapy arm and re-treatments at defined time points to any additional areas of nonperfusion demonstrated on repeat widefield FA.

Although visual results with combination therapy in the DAVE trial were not statistically inferior to monotherapy, there was no signal that the addition of targeted peripheral laser provided benefit to visual or treatment burden outcomes. Although not statistically significant, a trend toward decreased vision was noted in the combination arm. In the first year of the DAVE trial, there was no statistical difference in PRN ranibizumab injections between the 2 groups, but during the second year and overall through month 36, the combination therapy arm required statistically more PRN injections than the monotherapy arm. Furthermore, despite the use of targeted photocoagulation guided by widefield FA, the GVFs seemed to be suppressed more in the combination therapy arm.

A possible theory as to why there was no observed benefit of the targeted laser applied in DAVE trial is based on the work of Curcio et al demonstrating the posterior pole density of photoreceptors in contrast to the peripheral retina. Most metabolic demand across the retina is within the posterior pole, within retina that is too valuable for visual function to consider laser ablation (Fig 5). Additionally, nonperfusion on widefield FA in some cases may correspond with tissue that is dead rather than under hypoxic stress; in these cases, the potential benefits of TRP may be limited. In the DAVE protocol, anterior chamber paracenteses were performed at each intravitreal injection, and further analysis may allow correlation between nonperfusion and the effects of peripheral laser on cytokine levels over time to assess how effective the laser was at reducing levels of key growth factors such as VEGF.

Figure 5Widefield fluorescein angiography (FA) image demonstrating dense targeted retinal photocoagulation to approximately 78% of the total retinal surface. Overlying rod and cone photoreceptor density data, adapted from Curcio et al, of the retina posterior to the ablation zone revealed that this remaining 22% of surface area actually represents 47% of the 96.6 million total photoreceptors in the average retina.

Although TRP did not seem to decrease treatment burden or improve vision outcomes, it is likely that TRP decreased the development and morbidity of neovascular complications. Five eyes (25%) in the monotherapy arm demonstrated new PDR-associated neovascularization, with 2 of these eyes demonstrating neovascular glaucoma requiring surgical intervention. In comparison, none of the eyes in the combination therapy arm demonstrated the growth of new PDR-associated neovascularization. Our current recommendation is to treat DME in eyes with extensive peripheral retinal nonperfusion with anti-VEGF injections and to consider TRP in eyes with neovascularization or in patients with demonstrated poor compliance.

The DAVE trial was designed as a pilot trial, and we hypothesized that targeting the nonperfused peripheral retina would decrease vasoactive cytokine production, which would lead to a reduced need for PRN anti-VEGF injections in the management of DME. Over the entire prospective 36-month study, there was no evidence to support that targeted laser photocoagulation decreased the anti-VEGF injection burden.

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Article info

Publication history

Published online: January 11, 2018

Accepted: November 20, 2017

Received in revised form: September 28, 2017

Received: May 23, 2017

Manuscript no. 2017-1186.

Footnotes

Financial Disclosure(s): The author(s) have made the following disclosure(s): D.M.B.: Consultant – Genentech/Roche, Alcon/Novartis, Allergan, Clearside Biomedical, Optos/Nikon, Heidelberg Engineering, Aerpio, Allegra, Regeneron/Bayer; Financial support - Genentech

T.P.W.: Consultant – Genentech/Roche, Alcon/Novartis, Allergan, Clearside Biomedical, Heidelberg Engineering; Financial support – Genentech

R.Y.K.: Consultant – Genentech/Roche, Alcon/Novartis, Allergan, Clearside Biomedical, Heidelberg Engineering; Financial support – Genentech

C.C.W.: Consultant – Genentech/Roche, Alcon/Novartis, Allergan, Clearside Biomedical, Heidelberg Engineering, Aerpio, Regeneron/Bayer; Financial support – Genentech

Supported by Genentech, Inc., South San Francisco, California. The funding organization had no role in the design or conduct of this research.

HUMAN SUBJECTS: Human subjects were included in this study. Institutional review board/ethics committee approval (Sterling IRB, Atlanta, GA) was obtained for this study and written, informed consent was obtained from all participants. The study was performed in accordance with the tenets of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability (HIPPA) Act of 1996.

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Conception and design: Brown, Wong, Wykoff

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Data collection: Brown, Ou, Wong, Kim, Croft, Wykoff

Obtained funding: none

Overall responsibility: Brown, Ou, Wong, Kim, Croft, Wykoff

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Figures

Figure 1Representative widefield fluorescein angiography (FA) images of targeted retinal photocoagulation (TRP) applied to nonperfused peripheral retina in the combination therapy arm. **A**, Baseline widefield FA image demonstrating extensive nonperfusion. **B**, Month 6 widefield FA image demonstrating TRP and shoulder zones of residual nonperfusion that then were targeted with additional TRP (*red circles*). **C**, Month 27 widefield FA image showing heavy TRP applied peripherally with sparing of macula.

Figure 2Graph showing mean Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) through month 36.

Figure 3Graph showing mean central retinal thickness through month 36.

Figure 4Bar graph showing the distribution of the total number of injections administered through month 36 in the monotherapy and combination therapy arms.

Figure 5Widefield fluorescein angiography (FA) image demonstrating dense targeted retinal photocoagulation to approximately 78% of the total retinal surface. Overlying rod and cone photoreceptor density data, adapted from Curcio et al, of the retina posterior to the ablation zone revealed that this remaining 22% of surface area actually represents 47% of the 96.6 million total photoreceptors in the average retina.

Tables

Table 4Adverse Events