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A Prospective Randomized Comparative Dosing Trial of Ranibizumab In Bevacizumab-Resistant Diabetic Macular Edema: The REACT Study

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Abstract

Purpose—To assess the efficacy of ranibizumab for persistent diabetic macular edema (DME) previously treated with bevacizumab and compare monthly vs treat-and-extend (TAE) dosing.

Design—12-month, open-label, prospective randomized comparative dosing study.

Participants—27 participants with persistent foveal-involving DME recently treated with bevacizumab.

Methods—All subjects were to receive three initial monthly 0.3 mg ranibizumab injections before randomization to monthly (n=15) or TAE (n=12) injection protocols over 12 months. Treatment interval was extended by two weeks up to a maximum interval of 12 weeks in the TAE group if central subfield thickness (CST) was $\leq 300 \mu\text{m}$ or complete absence of intraretinal or subretinal fluid on the macular cube was observed. Follow-up interval was decreased by 2 weeks if CST increased above $300 \mu\text{m}$ with associated intraretinal and/or subretinal fluid.

Main Outcome Measures—Change in Early Treatment of Diabetic Retinopathy Study (ETDRS) best corrected visual acuity (BCVA), CST, adverse events.

Results—Prior to study enrollment, subjects received an average of 8.6 bevacizumab injections. At month 12, mean ETDRS BCVA improved by + 5.3 letters ($p < 0.05$) and mean CST decreased by $-99.6 \mu\text{m}$ ($p < 0.01$) in all patients. At study exit, 18.5 % of subjects gained ≥ 3 lines of vision and 3.7% of subjects lost ≥ 3 lines. Patients treated via the TAE protocol gained +8.4 letters and

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decreased CST by $-120.2\ \mu\text{m}$ whereas those treated by monthly injection gained $+2.7$ letters and decreased CST by $-83.1\ \mu\text{m}$ at month 12.

Conclusions—Following conversion to ranibizumab in eyes with persistent DME refractory to bevacizumab, significant functional and anatomic improvements were noted. Visual and anatomical outcomes were similar in TAE and monthly treatment protocols.

Introduction

Diabetic retinopathy (DR) develops in approximately 1 out of 3 diabetics and is the leading cause of blindness worldwide in working age adults of 20–74 years¹. While DR can lead to various secondary complications, diabetic macular edema (DME) remains the most common cause of vision loss¹. DME is an advanced complication of DR characterized by fluid accumulation in the macula and eventual central vision loss. Historically, laser photocoagulation has been the mainstay therapy for DME since the 1980s². However, the recent development of vascular endothelial growth factor (VEGF) inhibitors have supplanted laser as the typical first-line option for DME patients^{3–6}.

VEGF inhibitors commonly used for management of DME include bevacizumab, ranibizumab, and aflibercept. Ranibizumab (Lucentis; Genentech, South San Francisco, California) is a humanized monoclonal antibody fragment (Fab) lacking an Fc region, which became the first VEGF inhibitor approved by the Food and Drug Administration (FDA) in 2012 for treating DME following RISE & RIDE phase III clinical trials⁴. Off-label bevacizumab (Avastin; Genentech), a full-length humanized monoclonal antibody, has also demonstrated clinical utility with improvement in visual acuity and reduction in macular edema^{5,7}. More recently, the recombinant fusion protein aflibercept (Eylea; Regeneron, Tarrytown, New York) gained FDA approval for treatment of DME in 2014 based on two phase 3 clinical trials, VIVID and VISTA⁶.

Although the VEGF inhibitors have represented a significant iterative improvement in the armamentarium for DME treatment, deficits in therapeutic response still exist. For example, 56.7 % of bevacizumab treated subjects in the BOLT study exhibited persistent DME despite 24 months of treatment^{4,8}. In addition, studies have suggested there may be a differential effect of the various anti-VEGF therapies in regards to anatomic and visual acuity outcomes.⁹ Limited data is currently available on the role of switching pharmacotherapies in treatment-resistant DME. The question of whether to switch patients to another therapeutic agent is a commonly encountered challenge in clinical practice.

Additionally, optimal treatment regimens remain unclear. Clinicians rarely treat patients using the fixed monthly dosing regimens examined in RISE/RIDE studies. Instead, a recent survey suggested that the most frequent treatment regimens of intravitreal anti-VEGF injections are either as-needed (pro re nata [PRN]) or treat-and-extend (TAE) approach¹⁰. The role for TAE dosing in DME remains unclear and further research is needed to better define the efficacy and role for TAE regimens^{11,12}.

The Safety and Efficacy of Intravitreal Ranibizumab for Diabetic Macular Edema Previously Treated with Intravitreal Bevacizumab: A Randomized Dual-Arm Comparative

Dosing Trial: REACT Study is a 12-month, prospective, interventional, randomized dose-comparison trial of ranibizumab intravitreal therapy in eyes with treatment-resistant DME previously treated with bevacizumab. The purpose of REACT was to assess the impact of switching to ranibizumab therapy and to compare two treatment regimens (e.g., monthly, TAE).

Methods

Study Design

REACT (NCT#:01982435) is an IRB-approved 12-month, open-label, prospective, randomized IND trial evaluating ranibizumab in eyes with DME previously treated with bevacizumab comparing monthly and treat-and-extend dosing. All subjects provided written informed consent for participation in the study.

Study inclusion criteria were as follows: 1) Persistent foveal-involving DME confirmed by intraretinal and/or subretinal fluid by SD-OCT in the study eye at study entry; 2) ETDRS BCVA of 20/25 to 20/320 in the study eye; 3) History of at least 6 previous bevacizumab injections for DME in the last 12 months prior to study entry; 4) At least 2 bevacizumab injections within 10 weeks of study entry; and 5) At least 1 bevacizumab injection within 6 weeks of study entry.

The key exclusion criteria are history of vitrectomy, corneal transplant, trabeculectomy, surgery for retinal detachment, intravitreal/periocular steroid treatment within 3 months of study entry, focal/grid laser or panretinal photocoagulation treatments within 3 months of study entry, or any other intraocular surgery within 3 months of study initiation in the study eye. Subjects were also excluded on the basis of coexistent retinal diseases in the study eye (e.g., age-related macular degeneration, inherited retinal diseases), history of other retinal vascular disease (retinal vein occlusion, retinal artery occlusion), significant media opacities in study eye, active intraocular or periocular inflammation, active infection in either eye, and active scleritis or episcleritis in either eye. Additional intravitreal or periocular pharmacologics were not allowed in the study eye during the study, including but not limited to aflibercept, and steroids. Fellow eyes that developed DME during the study period or have DME at study entry were treated with ranibizumab at investigator discretion.

Visits and Assessments

All subjects were randomized into two treatment groups utilizing a randomization table (Figure 1). Monthly treated patients were given monthly 0.3 mg ranibizumab for 12 months. Subjects in the TAE group were initially treated monthly with 0.3 mg injections for three months before switching to a TAE protocol for the next 9 months. Follow-up intervals in the TAE protocol were determined with SD-OCT based information. If CST was $\leq 300 \mu\text{m}$ or complete absence of intraretinal or subretinal fluid on the macular cube was observed, the follow-up interval was increased by 2 weeks to a maximum interval of 12 weeks. If on subsequent follow-up visits, CST increased above $300 \mu\text{m}$ with associated intraretinal and/or subretinal fluid, the interval was reduced by 2 weeks.

At each scheduled study visit, ranibizumab was administered for the study eye. Each subject underwent standardized ETDRS refraction, SD-OCT (Cirrus HD-OCT, Zeiss, Oberkochen, Germany) and intraocular pressure measurement on both eyes. Ultra-wide fluorescein angiography (UWFA) images were taken for both eyes at baseline, months 3, 6, and 12 using an Optos-200Tx system (Optos, Scotland).

Study Endpoint

Key efficacy study endpoints included change in BCVA from baseline at 6-months and 12-months, eyes experiencing 3 lines or more visual acuity gain/loss, percentage of eyes with BCVA of 20/40 or better at 12-months, and change in CST from baseline at 6 and 12 months. The incidence of ocular adverse events, systemic adverse events, and serious adverse events (SAEs) were recorded to evaluate safety. AE reports were generated by study coordinators through nondirective questioning, lab testing, comprehensive eye exams, or other means and recorded in case report forms.

Statistical Analysis

Measures were summarized using means, range and standard error of the means (SEM). Two-sided paired t-tests and two-sided unpaired t-tests were respectively conducted to analyze efficacy endpoints between study initiation to end, and between monthly and TAE injection regimens. Patients who exited the study early were accounted by using a last observation carried forward approach. Chi-squared analysis was used to assess significant differences in OAE frequency. All analyses were performed using GraphPad Prism 5 (GraphPad Software, La Jolla, California, USA) with a significance level of 0.05 being assumed for all tests.

Results

In total, 27 subjects were enrolled in REACT with 15 being randomized to monthly injections and 12 in the TAE group (Table 1). The mean overall pre-enrollment number of bevacizumab injections was 8.6 ± 0.7 (range 6–20). At baseline, mean ETDRS BCVA was 20/51 (ETDRS letter score 64.7 ± 11.0). Mean baseline CST and macular volume across all subjects were $418.6 \pm 140.0 \mu\text{m}$ and $11.9 \pm 1.7 \text{ mm}^2$, respectively. Thirty-three percent (9) of subjects were 20/40 or better at baseline while 3.7% (1) of subjects were 20/200 or worse. Overall, there were no statistically significant differences between monthly and TAE groups in terms of demographic or study eye characteristics (Table 1).

Treatment Frequency in Comparative Design Groups

The mean overall number of ranibizumab injections received was 9.9 ± 0.4 . Subjects receiving monthly injections underwent 10.9 ± 0.5 injections while those in the TAE group received 9.6 ± 0.7 injections. Ranibizumab injection frequency between both treatment groups was not statistically significant ($p=0.21$).

Of the 12 subjects in the TAE group, 8 patients (66%) met criteria to extend beyond the baseline 4-week interval at any time during the study. Seven of 8 subjects were successfully

extended to 8 weeks or longer, including 5 that were extended to 10–12 week intervals. Representative anatomic responses in the TAE group are shown in Figure 2.

Impact on Visual Function

Across all subjects, mean ETDRS BCVA score significantly improved by +5.3 letters at month 12 ($p<0.05$). At study end, the monthly treatment group improved by a mean of +2.7 letters ($p=0.28$). The TAE group experienced a mean of +8.4 letters ($p<0.05$). There were no significant differences in visual acuity gain between the two groups at study completion.

After a year of treatment, 18.5% of subjects gained 3 lines of vision (+15 letters) and 3.7% of subjects lost 3 lines (–15 letters) from baseline. Additionally, the proportion of subjects with better than 20/20 and 20/40 vision at study completion increased from 0.0% to 14.8% and 33.3% to 40.7%, respectively. The number of subjects with vision worse than 20/100 decreased from 11.1% at study initiation to 3.7% by study termination.

At study end, the proportion of monthly and TAE treated subjects who gained +15 letters were 6.7% and 25% respectively (Figure 3). 6.7% of monthly treated subjects lost –15 letters or more, while none in the TAE group did. The proportion of monthly treated subjects with better than 20/20 and 20/40 vision increased from 0.0% to 13.3% and 33.3% to 40.0% respectively. Patients in the TAE group with better than 20/20 and 20/40 vision increased from 0.0% to 16.7% and 33.3% to 41.7% respectively. Patients with vision worse than 20/100 decreased from 13.3% to 6.7% in the monthly group whereas the TAE group decreased from 8.3% to 0.0% by study end.

Impact on Retinal Anatomy

Across all subjects, mean CST improved significantly from 419.4 μm to 319.9 μm (–99.6 μm , $p<0.01$) at study completion. Subjects in the monthly group improved from 400.1 μm to 317.0 μm (–83.1 μm , $p=0.10$) at month 12 while subjects under the TAE group improved from 443.6 μm to 323.4 μm (–120.2 μm , $p<0.01$). Macular volumes as determined by SD-OCT decreased across all subjects from 11.9 mm^3 to 10.8 mm^3 (–1.1 mm^3 , $p<0.01$) after 12 months. In patients receiving monthly IRIs, macular volumes decreased from 11.8 mm^3 to 10.8 mm^3 (–1.00 mm^3 , $p=0.06$) while patients under TAE protocol decreased from 12.0 mm^3 to 10.7 mm^3 (–1.3 mm^3 , $p<0.01$).

Qualitative grading of SD-OCT images was performed to identify anatomical changes in intraretinal and subretinal fluid. At baseline, 100% of patients presented with intraretinal fluid and 18.5% had subretinal fluid on SD-OCT. At month 12, 92.6% of patients exhibited intraretinal fluid while only 7.4% of patients had subretinal fluid. The proportion of monthly treated subjects with subretinal fluid decreased from 20% to 6.6% whereas the TAE group decreased from 16.7% to 8.3% at study end. Anatomic response rate was quite variable. In select subjects, there was a dramatic and rapid reduction in macular edema following a single ranibizumab injection (Figure 4A). In others, there was more measured, but consistent response over time (Figure 4B).

Impact on Angiography

Qualitative analysis of UWFA images was performed to identify retinal vascular pathology, specifically by observing the presence of vascular leakage, neovascularization, macular ischemia, and peripheral ischemia. At baseline, vascular leakage and neovascularization were identified in 92.6% and 7.4% of subjects respectively. After 12 months of ranibizumab treatment, 85% of patients demonstrated vascular leakage, and 3.7% exhibited neovascularization. The prevalence of macular ischemia was 33.3% at baseline and remained stable at study completion. Lastly, the proportion of peripheral ischemia observed in subjects increased from 66.7% at baseline to 70.3% at month 12. Although the incidence of “any” leakage remained stable at month 12. Subjects demonstrated overall improvement in the burden of angiographic leakage and microaneurysms (Figure 5).

Safety and Adverse Events

The most commonly occurring ocular AEs affecting study eyes included blurry vision, dry eye, elevated IOP, and flashes (Table 2). Despite 7 isolated episodes of elevated IOP, there were no statistically significant differences in mean IOP at 12 months compared to baseline in either treatment groups (Monthly: $p=0.13$, TAE: $p=0.25$). There were no statistically significant differences in ocular AE incidence between monthly and TAE treatment groups (Chi-squared, $p>0.05$). Serious systemic thromboembolic AEs included 1 case each of acute stroke and unstable angina which occurred in subjects receiving monthly IRIs. Twenty-four of 27 (89%) subjects completed the full 12 months of the study. One subject discontinued following a stroke. Two other subjects discontinued due to requirements to change care location.

Discussion

In this prospective randomized trial of persistent-foveal involving DME following bevacizumab therapy, switching to 0.3 mg ranibizumab was followed by statistically significant functional and anatomic improvements after 1 year of treatment. Subjects at study completion exhibited an average increase in ETDRS BCVA of +5.3 letters ($p<0.05$), a mean decrease of $-99.6 \mu\text{m}$ in CST ($p<0.01$) and -1.1 mm^3 ($p<0.01$) in macular volume. Additionally, 18.5% of subjects gained at least 15 ETDRS letters (3 Snellen lines) following a year of ranibizumab treatment, with only 1 patient losing greater than 15 letters compared to baseline. While the exact mechanism for functional and anatomic improvements following the switch from bevacizumab to ranibizumab remains unclear, possible explanations include smaller molecular size, higher potency, regression to the mean, previous under treatment, and increased binding affinity of ranibizumab.

Both regimens demonstrated similar functional and anatomic improvements. Although in the first year there were no significant difference in injection frequency between the 2 groups, a more significant decrease in injection frequency would likely be observed in the TAE group had REACT been extended beyond 1 year. Of the 12 patients in the TAE group, 2 patients were extended to 8 weeks or more, and 5 patients were extended to 10–12 weeks at the end of the study. While this suggests similar results with both dosing regimens, the small sample size limits the ability to draw definitive conclusions regarding the two dosing regimens.

Subjects in the TAE dosing group did not all respond equally to ranibizumab. One patient demonstrated significant functional and anatomic improvement after the first ranibizumab injection but was unable to be extended beyond 6 weeks without returning to baseline (Figure 4A). Other subjects demonstrated slow and progressive improvements throughout the study (Figure 4B), or were able to be rapidly extended to 12 weeks without relapsing (Figure 2A). The mechanisms driving differing ranibizumab response are likely also driving the initial non-responsiveness or loss of responsiveness to specific VEGF inhibitors in treatment refractory DME. Possible explanations for these phenomena include the variability inherent in the course of DME and the response to treatment, tachyphylaxis and drug tolerance. Tachyphylaxis develops with drugs given repeatedly over a short period whereas tolerance is characterized by slow loss of efficacy. While tachyphylaxis does not respond to increased drug dosages, tolerance can be overcome with higher doses¹³. Potential solutions for tachyphylaxis and tolerance includes briefly pausing treatment, increasing drug dosage, combining drugs with different mechanisms of action, or switching amongst different VEGF inhibitors¹³.

Several studies in the AMD literature have examined the role of switching VEGF inhibitors in management of nonresponders^{14–23}. However, significantly fewer studies have investigated switching to ranibizumab for refractory DME treated with bevacizumab. The ROTATE trial is a recent 12-month prospective study containing 30 eyes with persistent DME after bevacizumab treatment.²⁴ Ranibizumab injections were given monthly for the first 6 months before eyes received either monthly or PRN dosing regimens for the remaining 6 months. BCVA were +6.7 letters and +6.4 letters in monthly and PRN treated groups respectively at study end, and CST were –92 μ m and –127 μ m respectively at month 12. These results were consistent with the functional and anatomic improvements observed in REACT. However, there were a few differences in study design between ROTATE and REACT. The ROTATE had 6 initial mandated monthly ranibizumab injections for all eyes, whereas REACT only had 3 initial monthly injections. Secondly, ROTATE had compared monthly dosing to PRN dosing whereas REACT compared monthly dosing to a TAE regimen. For persistent DME, the REEF study (prospective trial of 43 patients) demonstrated improved visual and anatomic outcomes in patients previously managed by bevacizumab after switching to 3 monthly injections of 0.5 mg ranibizumab²⁵. Patients had mean reductions of 113 μ m and gain of 6.4 letters at month 3. Individuals with residual macular edema at month 3 received three additional monthly high-dose ranibizumab injections (2.0 mg) and gained an additional +2.0 letters with an additional reduction of 51.8 μ m in CST by month 6. Additional retrospective reviews have also suggested the potential improvement with ranibizumab for eyes with persistent DME following bevacizumab therapy.^{26–28} Although TAE regimens in AMD have been well-described, few studies have evaluated TAE in DME. The TREX-DME 1-year outcomes demonstrated similar visual and anatomic outcomes utilizing a TAE regimen compared to a monthly regimen.¹²

There are limitations to the REACT study that warrant further discussion. The relatively small sample size risks under-powering this study and potentially missing differences between the two dosing groups. In addition, the 1-year duration of this study is too short to appreciate significant differences in ranibizumab injection frequency between monthly and TAE dosing regimens. The lack of a control group is an important limitation to recognize

that also limits the conclusions to more definitively attribute the improvements in visual acuity and macular edema to the switch to ranibizumab rather than the specific dosing regimen. The more structured and rigorous treatment interval may have been the key factor in improvement rather than the switching the drug.²⁹ In order to minimize this risk, subjects underwent treatment with at least 6 bevacizumab injections in the year prior to enrollment including at least 2 in the 10 weeks prior to enrollment.

Despite these limitations, REACT is a prospective study that provides efficacy and safety data following the switch to ranibizumab in treatment-resistant patients. In this report, conversion to ranibizumab was followed by significant visual and anatomic improvements at study completion. Dosing with a TAE regimen appeared successfully to reduce macular edema and improve visual acuity at similar rates to the monthly group. Future research in switching therapy should include a control arm that maintains the previous therapy. In addition, longer term follow-up is needed to better assess the role of TAE in treatment-resistant DME.

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Figure 1. REACT Study Design

Abbreviations: SD-OCT, spectral domain optical coherence tomography; UWFA, ultra-widefield fluorescein angiography

Figure 2. Anatomic Response following Switch to Ranibizumab

Representative foveal SD-OCT images of subjects demonstrating A) Subject exhibiting significant subretinal fluid and intraretinal fluid at study enrollment. Following 3 monthly ranibizumab injections and subsequent early extension, complete resolution of fluid is seen at month 6. Maximal extension to 12 weeks was tolerated with continued resolution of fluid at study exit. B) Different subject demonstrating subretinal fluid and intraretinal fluid at baseline. Following initial monthly therapy, near complete resolution of intraretinal fluid and complete resolution of subretinal fluid achieved at 6 –months. Initial treatment interval extension is well-tolerated, but extension to a 10-week interval results in recurrent edema at study exit visit.

Figure 3. Functional Outcomes following Switch to Ranibizumab

Visual acuity outcomes among monthly, treat-and-extend, and overall groups from baseline to study exit.

Figure 4. Variations in Response to Ranibizumab in Bevacizumab-Resistant Eyes

Representative examples of variable anatomic response among REACT subjects. A) Subject exhibited rapid functional and anatomical improvements after the first ranibizumab injection that was maintained throughout the study. B) Subject demonstrated slow, but persistent improvement in anatomy and function during regular treatment with ranibizumab therapy.

Figure 5. Angiographic Changes Following Treatment with Ranibizumab in Bevacizumab-Resistant Eyes

Representative early-phase (A) and late-phase (B) UWFA of a subject in the monthly treatment group at baseline and month 12. Green boxes highlight MA clusters no longer present at month 12.

Table 1

Baseline characteristics of patients enrolled within REACT trial. There were no differences between groups for any of the variables.

Baseline Characteristics	Total (n=27)	Monthly (n=15)	Treat and Extend (n=12)
Age, mean (SEM)	63.1 (6.1)	62.5 (6.0)	63.8 (6.4)
Male, n (%)	11 (41%)	5 (33%)	6 (50%)
OD study eye, n (%)	16 (59%)	10 (66%)	6 (50%)
Diabetic Retinopathy Status, n	Proliferative: 9, Non-Proliferative: 18	Proliferative: 5, Non-Proliferative: 10	Proliferative: 4, Non-Proliferative: 8
Average bevacizumab injections prior to study, mean (SEM)	8.6 (0.7)	8.7 (0.8)	8.5 (1.1)
ETDRS BCVA letter score, mean (SEM, snellen equivalent)	64.7 (11.0, 20/51)	65.1 (9.8, 20/50)	64.2 (12.8, 20/52)
Central subfield thickness (μm), mean (SEM)	418.6 (140.0)	398.6 (136.9)	443.6 (145.6)
Macular Volume, mean (SEM)	11.9 (1.7)	11.7 (1.7)	12.0 (1.9)
Intraocular Pressure (IOP), mean (SEM)	18.8 (4.7)	19.2 (6.1)	18.2 (2.1)
Percentage of subjects 20/40 or better (n)	33.3% (9)	33.3% (5)	33.3% (4)
Percentage of subjects 20/100 or worse (n)	11.1% (3)	13.3% (2)	8.3% (1)

Table 2

Frequency of study eye ocular adverse events through month 12 of the REACT study.

Ocular AE, n (Incidence)	Total (n=27)	Monthly (n=15)	Treat and Extend (n=12)
Blurry Vision	14 (51.85%)	9 (60%)	5 (41.67%)
Elevated IOP	7 (25.93%)	4 (26.67%)	3 (25%)
Flashes	6 (22.22%)	3 (20%)	3 (25%)
Vitreous Floaters	5 (18.52%)	3 (20%)	2 (16.67%)
Dry Eyes	5 (18.52%)	3 (20%)	2 (16.67%)
Redness	3 (11.11%)	1 (6.67%)	2 (16.67%)
Pruritus	2 (7.41%)	2 (13.33%)	0 (0%)
Tearing	2 (7.41%)	1 (6.67%)	1 (8.33%)