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Randomized Clinical Trial Evaluating Intravitreal Ranibizumab or Saline for Vitreous Hemorrhage from Proliferative Diabetic Retinopathy

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Abstract

Objective—To evaluate intravitreal ranibizumab compared with intravitreal saline injections on vitrectomy rates for vitreous hemorrhage (VH) from proliferative diabetic retinopathy (PDR).

Main Outcome—Cumulative probability of vitrectomy within 16 weeks.

Methods—Study eyes had VH from PDR precluding panretinal photocoagulation (PRP) completion. Eyes were randomly assigned to 0.5-mg ranibizumab (N = 125) or saline (N = 136) at baseline, 4, and 8 weeks.

Results—Cumulative probability of vitrectomy by 16 weeks was 12% with ranibizumab versus 17% with saline (difference 4%, 95% confidence interval –4%–13%) and of complete PRP without vitrectomy by 16-weeks was 44% and 31% respectively ($P = 0.05$). The mean ($\pm$ SD) visual acuity improvement from baseline to 12 weeks was 22 $\pm$ 23 letters and 16 $\pm$ 31 letters respectively ($P = 0.04$). Recurrent VH occurred within 16 weeks in 6% and 17% respectively ($P = 0.01$). One eye developed endophthalmitis after saline.

Conclusions—Overall the 16 week vitrectomy rates were lower than expected in both groups. This study suggests little likelihood of a clinically important difference between ranibizumab and

* A published list of the Diabetic Retinopathy Clinical Research Network investigators and staff participating in this protocol can be found in Appendix 1 with a current list and financial disclosures available at www.drcr.net

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saline on the rate of vitrectomy by 16 weeks in eyes with VH from PDR. Short term secondary outcomes including visual acuity improvement, increased PRP completion rates, and reduced recurrent VH rates suggest biologic activity of ranibizumab. Long term benefits remain unknown. Whether vitrectomy rates after saline or ranibizumab are different than observation alone cannot be determined from this study.

Application to Clinical Practice—Intravitreal ranibizumab does not appear to reduce vitrectomy rates compared with saline for VH from PDR.

Introduction

Diabetic retinopathy is the leading cause of visual loss and new-onset blindness in the United States. The prevalence of diabetic retinopathy in patients older than 40 years of age with diabetes exceeds 40%, with 8.5% developing vision-threatening complications, including proliferative diabetic retinopathy (PDR), severe non-proliferative diabetic retinopathy, or macular edema.¹ PDR can lead to vitreous hemorrhage which not only affects vision substantially but also can preclude performing panretinal photocoagulation (PRP), the standard treatment for PDR. Even after PRP is initiated for PDR, at least 5% of cases develop vitreous hemorrhage, often requiring vitrectomy.² According to a recent survey of retina specialists, vitreous hemorrhage from PDR is one of the most common reasons for vitrectomy in the United States.³

In mild to moderate cases of vitreous hemorrhage, PRP is performed when possible to achieve regression of new vessels or at least stabilization of the neovascularization in order to decrease the probability of subsequent vitreous hemorrhage while spontaneous absorption of the hemorrhage occurs.⁴ In cases in which the hemorrhage is too dense to apply PRP, vitrectomy is considered to remove the hemorrhage and provide a clear media for application of PRP (usually as endolaser photocoagulation) as well as eliminate extensive neovascularization and relieve traction retinal detachments. Many advances in instrumentation and technique have resulted in a dramatic reduction in complications over the last few decades, but surgical complications remain including neovascular glaucoma, retinal detachment, fibrinoid syndrome, endophthalmitis, and hypotony with subsequent phthisis bulbi.⁵ In addition, recovery to normal activities following vitrectomy can take several days, weeks or even months, thus affecting an individual's ability to function and work.

The rationale for anti-vascular endothelial growth factor (anti-VEGF) treatment for vitreous hemorrhage from PDR is based on several studies which show that VEGF is a major causative factor in eye diseases characterized by neovascularization or increased vascular permeability such as diabetic retinopathy.^{6–15} Injections of VEGF into normal primate eyes induce pathological findings that closely resemble diabetic retinopathy, including neovascularization and retinal vascular permeability changes.^{14, 16, 17} Vitreous samples from patients with PDR have elevated VEGF concentrations which are reduced following successful PRP.⁸ Inhibition of VEGF can reduce VEGF and diabetes-induced permeability.¹⁵ Small, uncontrolled case series have suggested that intravitreal anti-VEGF treatment causes short-term clearing of vitreous hemorrhage so that PRP may be applied

without having to perform vitrectomy.¹⁸ Based on the findings from these preliminary studies, there has been interest in using anti-VEGF drugs to treat eyes with vitreous hemorrhage due to PDR in which the vitreous hemorrhage precludes the ability to apply PRP. However, it is unknown whether apparent clearing of vitreous hemorrhage following anti-VEGF injections is due to anti-VEGF activity, the intravitreal injection alone, or both, because these reports were in the absence of an intravitreal injection of vehicle or saline as a control group to evaluate this possibility. A prior unpublished study in eyes with vitreous hemorrhage (ISTA) found that saline injected eyes were three times more likely to have visual acuity improvement at three months (36.3% vs. 11.1%) than eyes in the watchful waiting control group.¹⁹

To assess the efficacy and safety of anti-VEGF therapy as a treatment for vitreous hemorrhage due to PDR, the Diabetic Retinopathy Clinical Research Network (DRCR.net) conducted a randomized trial to compare intravitreal ranibizumab injections with intravitreal saline injections in eyes presenting with vitreous hemorrhage from PDR. This study was designed to determine whether intravitreal injections of ranibizumab would facilitate clearing of vitreous hemorrhage, thus avoiding vitrectomy and its potential complications. Compared with vitrectomy use of an intravitreal agent, which obviates the need for vitrectomy, would be preferable because of the reduced costs, reduced time to initiate treatment, reduced intervention time, relatively low risk of side effects, and reduced recovery time. Secondary analyses assessed the mean change in visual acuity, completion of PRP, vitreous hemorrhage recurrence and optical coherence tomography (OCT) signal strength.

Methods

This Phase III, double masked, randomized multicenter clinical trial was conducted by the DRCR.net at 61 sites in the United States. The study was in compliance with the policies described in the DRCR.net Policies document (www.drcr.net Accessed June 24, 2012), with ethical principles that have their origin in the Declaration of Helsinki and with the standards of Good Clinical Practice. Each study participant provided written informed consent to participate in the study. Study oversight was provided by an independent data and safety monitoring committee. The study is listed on www.clinicaltrials.gov, under identifier NCT00996437 (website registration date October 14, 2009) and the protocol is available on the DRCR.net website (www.drcr.net, Accessed July 24, 2012). Data reported were collected from June 2010 to March 2012. Key aspects of this study are detailed below.

Study Population

Eligible study participants were at least 18 years of age with type 1 or type 2 diabetes. Eligible eyes had vitreous hemorrhage presumed to be from PDR, causing vision impairment and precluding completion of PRP (or precluding assessment of completeness of prior PRP). Eyes requiring immediate vitrectomy for reasons such as rhegmatogenous or traction retinal detachment were not eligible. Other principal exclusion criteria for a study eye included vision of no light perception, neovascular glaucoma, iris neovascularization judged to be “active” by the investigator or angle neovascularization, history of intravitreal

anti-VEGF treatment for vitreous hemorrhage at any time in the past or for another indication in the prior two months, and prior vitrectomy.

Key Aspects of Study Design—After eligibility was determined and informed consent was obtained, study eyes were randomly assigned on the DRCR.net website, with equal probability, to either intravitreal 0.5 mg ranibizumab (Lucentis® Genentech, Inc, South San Francisco, CA) or intravitreal saline (0.9% sodium chloride injection, USP; Formatech, Inc., Andover, MA) injections or injections using a permuted blocks design stratified by site. Study visits occurred at 4, 8, 12 and 52 weeks. This paper reports only data through 16 weeks of follow-up unless otherwise specified.

Best-corrected electronic-Early Treatment Diabetic Retinopathy Study visual acuity test (E-ETDRS) was performed on the study eye by a certified technician at baseline and at each follow-up visit. At 12 weeks, protocol refraction was required only for the study eye. Baseline visual acuity could have been performed either pre- or post- dilation. OCT images were obtained on either time domain or spectral domain OCT machines by certified technicians at baseline and each follow-up visit for the study eye. If an insufficient view precluded obtaining an accurate OCT, only the signal strength was recorded. Additional testing included measurement of hemoglobin A1c and blood pressure at baseline. At baseline and at each follow-up visit, slit lamp examination, fundus examination following pupil dilation, and measurement of intraocular pressure were performed. If vitreous hemorrhage precluded ability to assess for traction or rhegmatogenous retinal detachment on clinical exam, then a B-Scan ultrasound also was performed.

Eyes received an injection of saline or 0.5 mg ranibizumab at randomization, four weeks, and eight weeks using a masked vial provided by the Coordinating Center that was identified by number only. The injection was deferred at four and eight weeks if vitrectomy had already been performed, the hemorrhage had sufficiently cleared such that complete PRP could be given (or it was determined that complete PRP was already given), or an adverse event occurred from a prior intravitreal injection. Injections were preceded by a povidone iodine prep of the conjunctiva. Use of antibiotics in the pre-injection, peri-injection, or post-injection period was not required and was at investigator discretion. Study participants and all study personnel were masked to treatment group assignment throughout the study.

At each visit the study eye was assessed to determine whether vitrectomy was indicated. The decision to perform vitrectomy was based on study guidelines. Prior to the eight week visit, vitrectomy was not to be performed unless one of the following was present: (1) traction retinal detachment involving (within 1 disc diameter) or actively threatening the macula; (2) rhegmatogenous retinal detachment; (3) neovascular glaucoma resulting in increased intraocular pressure that could not be controlled medically, angle neovascularization, or progressive neovascularization of the iris; and (4) ghost cell glaucoma resulting in increased intraocular pressure that could not be controlled medically. Between the 8 week-visit and 16 week endpoint, vitrectomy was not required, but could have been performed, based on investigator discretion, if there was failure of substantial clearing of the vitreous hemorrhage such that the participant's need for vitrectomy and its associated benefits outweighed its

risks. If vitrectomy was performed prior to 16 weeks of study follow-up, pre-operative treatment with an anti-VEGF drug was not permitted except as part of the scheduled treatment per randomization since such treatment might influence the decision to proceed to vitrectomy. Peri- and post-operative treatment with an anti-VEGF drug was only permitted if the vitrectomy was performed after the 12-week visit in order to prevent 'double-dosing'.

PRP was to be performed as soon as possible after the baseline injection until "complete" PRP had been performed. For purposes of this study, "complete" PRP was defined by the protocol as 500 μ m size burns on the retina placed no further than one to two burns widths apart beginning $\sim$ 3000 μ m from the macular center and extending to the equator for 12 clock hours (or at least 10 clock hours if vitreous hemorrhage precluded sufficient treatment or evaluation of all 12 clock hours). If the vitreous hemorrhage cleared and it was determined that the eye had already received "complete" PRP, further PRP treatment was not required.

Statistical Methods—The primary outcome was a treatment group comparison of the cumulative probabilities of vitrectomy performed within 16 weeks (112 days) of randomization. The sample size was estimated initially to be 126 eyes, one eye per participant, for vitrectomy rates of 60% in the saline injection group vs. 30% in the ranibizumab injection group, resulting in 90% power for a two-sided test with type I error rate equal to 5%. A pre-planned interim analysis with sample size re-estimation using the conditional power-based method of Li et al was conducted when approximately 60 subjects reached 16-weeks of follow-up (the primary outcome endpoint).²⁰ Following the pre-planned interim analysis, the sample size was increased to 260 study eyes, the pre-specified maximum. The criterion for declaring efficacy at the final analysis was set to $P < 0.0365$ to account for alpha spent by the interim efficacy analysis and sample size re-estimation in order to control the overall type I error at 5%. P values for secondary outcomes are provided as guides to interpretation of the data, with $P < 0.01$ suggesting some evidence of a difference.

Primary Analysis—The primary analysis followed the intent-to-treat principle and included all randomized eyes. The cumulative probabilities of vitrectomy by 16 weeks (112 days) in each group were computed using the life-table method. The treatment group comparison was made using the log-rank test.²¹ Data were censored at the time point of the participant's last completed visit. Imbalances between groups in important covariates were not expected; however, Cox proportional hazards modeling was performed to investigate the effect of treatment on time to vitrectomy, while simultaneously adjusting for other possibly influential variables.²²

Secondary Outcomes—The proportion of eyes with "complete" PRP by 16 weeks in the absence of vitrectomy was computed using the life-table method and treatment groups were compared using the log-rank test. Time to event was defined for this purpose as date from randomization to completion of PRP or date when the hemorrhage had cleared such that the investigator could determine that PRP already had been completed. Eyes that still had vitreous hemorrhage which precluded determination of "complete" PRP were considered at risk for purposes of this analysis. Eyes that received PRP after vitrectomy were not

considered as events, but were considered still at risk at the time of analysis, as without vitrectomy, these subjects would have unlikely been able to complete PRP within the time frame of the analysis, and counting them as censored at the time of vitrectomy would preferentially eliminate subjects at lowest risk of the event from the at risk population, resulting in overestimation of PRP completion rate.

Binary outcomes were analyzed using Fisher's exact test or logistic regression with adjustment for the baseline level of the outcome. Continuous outcomes were analyzed using a longitudinal mixed regression model adjusting for baseline measures.²³ Time to event outcomes were analyzed using the log-rank test or Cox regression model adjusting for baseline factors. Linear assumptions were verified. The proportional hazard assumption was verified by introducing interaction terms of the factors with time and testing for significance.²¹ All *P* values are 2-sided. SAS version 9.1 (SAS Institute, Cary, NC) was used for all analyses. Adverse events reflect all events reported through February 21, 2012.

Results

Between June 2010 and October 2011, 261 study participants (mean age 58 ± 12 years; 52% women) were entered into this study at 61 clinical sites. The 261 study eyes were assigned randomly to either 0.5 mg ranibizumab injection ($N = 125$) or saline injection ($N = 136$). At baseline, 54% of study participants had prior PRP, 42% had prior treatment for DME and 65% had OCT signal strength equal to 0. Overall, the mean visual acuity letter score at baseline was 33 ± 29 (approximate Snellen equivalent 20/250) and the mean Hemoglobin A1c was $8.0\% \pm 1.7$. Baseline characteristics in the two treatment groups are shown in Table 1.

Follow Up

Visit completion status is presented in eFigure 1 (eFigure 1, <http://archophthalmol.com>). One participant died during the study from an unknown cause prior to the 16 week primary endpoint. Not including the one death, the 12-week visit was completed for 95% of study participants overall, with a 96% completion rate in the ranibizumab injection group and 95% completion rate in the saline injection group.

Treatments

All participants received the assigned treatment regimen at baseline except for one participant from the saline injection group who after consenting and being randomized decided not to receive an injection. This participant remained in the study but never received an injection. Among the study participants who completed the eight-week study visit and were required by protocol to receive three injections, 81 (84%) eyes in the saline injection group and 81 (94%) eyes in the ranibizumab injection group received all three required study injections at baseline, four weeks, and eight weeks. One participant from the saline injection group received an extra study injection at the 12-week follow-up visit when study treatment was not scheduled per protocol due to clinic error. Reasons for missed injections included the following: missed visit (8 eyes), adverse event precluding treatment (9 eyes),

subject refusal (2 eyes), treatment not needed according to investigator (1 eye), investigator and subject decided to wait and observe (1 eye) and opted for vitrectomy (2 eyes).

Eight study eyes received treatment for diabetic macular edema prior to the 16-week endpoint. This additional treatment was provided to four eyes from the saline injection group (one eye received intravitreal bevacizumab between the 12 and the 16 week time points and three eyes received macular laser photocoagulation) and four eyes from the ranibizumab injection group (two eyes received macular laser photocoagulation, one eye received intravitreal triamcinolone acetonide at the 12 week visit, and one eye received both intravitreal bevacizumab (8 weeks after last study injection) and intravitreal triamcinolone acetonide (12 weeks after last study injection).

Primary Outcome: Effect of Treatment on Vitrectomy by 16 weeks—As shown in Figure 1, by the 16-week primary outcome, the cumulative probability of vitrectomy was 12% for the ranibizumab injection group and 17% for the saline injection group (hazard ratio 0.74, 95% confidence interval [CI] 0.38 to 1.43, $P=0.37$). Of the 22 eyes in the saline injection group undergoing vitrectomy by 16 weeks, the vitrectomy was completed prior to the 8 week visit in 3 eyes (14%) as a result of traction retinal detachment in the macula, rhegmatogenous retinal detachment or participant insistence. Similarly, 3 of the 15 eyes (20%) in the ranibizumab injection group undergoing vitrectomy did so prior to 8 weeks as a result of traction retinal detachment in the macula, rhegmatogenous retinal detachment or neovascular glaucoma. For both treatment groups, the most frequent reason for vitrectomy performed between 8 and 16 weeks of follow-up was failure of substantial clearing of vitreous hemorrhage. Other reasons included traction retinal detachment in the macula, rhegmatogenous retinal detachment, neovascular glaucoma and participant insistence. An exploratory analysis of vitrectomy prior to 20 weeks was performed and showed similar results (eFigure 2, <http://archophthalmol.com>) to the data at 16 weeks (18% in the ranibizumab injection group compared with 23% in the saline injection group). After adjusting for age, Hemoglobin A1c, prior PRP, duration of vitreous hemorrhage, prior DME treatment, prior anti-VEGF treatment and lens status, time to vitrectomy remained similar between treatment groups. The difference at 16 weeks between treatment groups in cumulative probability of vitrectomy was 4% with a 95% confidence interval (–4%, 13%).

Secondary Outcomes—The cumulative probability of having a complete PRP and no vitrectomy by the 16-week follow up endpoint was 44% in the ranibizumab injection group compared with 31% in the saline injection group (Figure 2, hazard ratio 1.54, 95% CI: 1.03 to 2.30, $P=0.05$).

As shown in Table 2, the mean ($\pm$ SD) improvement in visual acuity from baseline to the 12-week follow-up visit, adjusting for baseline visual acuity, was 22 ± 23 letters in the ranibizumab injection group compared with 16 ± 31 letters in the saline injection group (adjusted difference = 5.9, 95% CI 0.3 to 11.6, $P=0.04$). A visual acuity letter score >68 (approximate Snellen equivalent 20/50 or better) and no vitrectomy occurred in 45% of participants in the ranibizumab injection group and 33% in the saline injection group ($P=0.08$, Table 3). The percentages of eyes with poor visual acuity (letter score <34 , approximate Snellen equivalent worse than 20/200) and very poor visual acuity (letter score

<4, approximate Snellen equivalent worse than 20/800) were 20% versus 27% ($P = 0.23$) and 11% versus 16% ($P = 0.27$), respectively (Table 3).

OCT signal strength was evaluated as a potential indicator of vitreous hemorrhage density in an exploratory analysis. In the ranibizumab injection group, among participants with a baseline OCT signal strength equal to zero, 51% of eyes had OCT signal strength greater than zero and no vitrectomy at the 12-week visit compared with 52% in the saline injection group (Table 4, $P = 0.87$).

Ocular Adverse Events—Ocular adverse events prior to the 16 week time point are summarized in Table 5. One study eye (0.74%, 95% CI: 0.02% to 4.0%) from the saline injection group had a culture-negative endophthalmitis related to the study injection. Recurrent vitreous hemorrhage was reported based on clinical examination in 6% in the ranibizumab injection group compared with 17% of eyes in the saline injection group ($P = 0.01$). Eight eyes (6%) in the ranibizumab injection group and 9 eyes (7%) in the saline injection group had a traction retinal detachment ($P > 0.99$). Rhegmatogenous retinal detachments were reported in one eye (<1%) in the ranibizumab injection group ($P > 0.99$) and 2 eyes (2%) in the saline injection group. A combination of traction and rhegmatogenous retinal detachment was reported in one additional eye in the ranibizumab injection group.

Thirteen percent and 14% of eyes in the ranibizumab and saline injection groups, respectively, had elevated intraocular pressure within the first 16 weeks of the study ($P = 0.86$). This was defined as either an increase of intraocular pressure >10 mm Hg, intraocular pressure >30 mmHg at any visit, prescribed intraocular pressure lowering medication at follow-up but not at baseline, or glaucoma surgery. Ghost cell glaucoma was reported prior to the 16-week visit for one eye in each group. Prior to the 16-week follow-up visit, one eye in the ranibizumab injection group and 4 eyes in the saline injection group had iris or angle neovascularization.

Systemic Adverse Events

Prior to the 16 week time point, there were no observed systemic adverse event differences among the two treatment groups that could not be attributed to chance alone. One participant (1%) in the ranibizumab injection group had a cardiovascular or cerebrovascular event according to Antiplatelet Trialists' Collaboration criteria prior to 16 weeks.²⁴ The number of hypertension-related events was 3 (2%) in the ranibizumab group versus 7 (5%) in the saline injection group.

Discussion

This study suggests little likelihood of a clinically important difference between intravitreal ranibizumab and saline on the rate of vitrectomy by 16 weeks in eyes with vitreous hemorrhage from PDR. In this study, for both treatment groups, the vitrectomy rates were lower than expected with observation alone. It is unknown whether observation alone would have resulted in a higher rate of vitrectomy or a slower rate of vitreous hemorrhage clearance than what was observed in this study with intravitreal ranibizumab or saline

injections. At the time of study design, an observation only arm was considered; however, there were concerns with feasibility of recruiting a sufficient number of subjects for a 3-arm study.

The rationale for using an intravitreal saline injection as the control group was to reduce the possibility that a benefit would be identified with ranibizumab that actually was due in part or completely to an effect from the injection of fluid itself rather than an anti-VEGF effect. Prior data support the concept that saline injections may result in clearing of vitreous hemorrhage faster than observation alone (ISTA, unpublished data).¹⁹ In addition, when the primary outcome is vitrectomy, as in this study, and is determined by the investigator and thus is a subjective determination, it is essential that complete masking of the investigator, study personnel and study participant be maintained during the study. This was best achieved using saline packaged in the same type of vial as ranibizumab, designed to try to make the two treatments indistinguishable to these study personnel and participants.

The rates of vitrectomy in both the ranibizumab and saline groups in this DRCR.net report were lower than projected when designing the study. Initial projections were based on the saline injection group of the ISTA trial in which approximately 60% of the eyes had persistent vitreous hemorrhage at 16 weeks. A more recent small prospective non-randomized trial reported vitrectomy rates in a bevacizumab treated group of 10%, similar to this trial. The same study reported a 45% vitrectomy rate with observation alone.²⁵ Additional evidence of the effect of bevacizumab on PDR comes from a larger retrospective study by Arevalo and colleagues, which showed total regression of neovascularization on fundus examination and fluorescein angiography.²⁶ However, none of these prior studies with anti-VEGF were randomized or compared the effects of intravitreal anti-VEGF therapy with saline injections. Of note, the duration of vitreous hemorrhage was less than 1 month in the majority of eyes in this study, in comparison with the prior studies in which the average duration of vitreous hemorrhage was longer. As a result of having substantially overestimated the control group rate when estimating sample size, the study may not have been sufficiently powered to detect a treatment group difference. Therefore, the interpretation of the confidence interval is critical. It is likely that the true difference in vitrectomy rates by 16 weeks between the ranibizumab group and saline group is between -4% and 13%. Therefore, the results are consistent with saline being slightly better than ranibizumab or ranibizumab being better than saline, but a large treatment group difference is unlikely.

The secondary outcomes, including better visual acuity (Table 2), fewer recurrent vitreous hemorrhages and increased chance of completing PRP (Figure 2) suggest at least a short-term biologic effect of intravitreal ranibizumab compared with intravitreal saline although secondary outcome differences may be due to chance alone. Additionally, since this study evaluated only the short-term effects of intravitreal injections on vitreous hemorrhage; it is not possible to determine whether the trends identified during the first 16 weeks on secondary outcomes continue over the long term.

Since a recent survey within the American Society of Retina Specialists revealed that one-third of retina specialists use anti-VEGF products frequently in eyes prior to vitrectomy, it

remains important to continue to evaluate the safety of its use in eyes with PDR.³ This study did not find an increase in the risk of a traction or rhegmatogenous retinal detachment from intravitreal ranibizumab in the setting of PDR (~8% in each group), which is consistent with prior controlled trials of intravitreal ranibizumab that also did not find an increased risk.^{27, 28} These findings do not support the conclusions from previously reported uncontrolled studies which raised some potential ocular safety concerns with respect to traction retinal detachment when considering the use of an anti-VEGF drug in eyes with vitreous hemorrhage from PDR.²⁹ Another potential safety concern of intravitreal anti-VEGF products in the presence of vitreous hemorrhage is ghost cell glaucoma.³⁰ However, this DRCR.net study did not find a similar safety problem when ranibizumab was compared with the intravitreal saline group; in both treatment groups one event of ghost cell glaucoma was reported.

In conclusion, this DRCR.net study suggests little likelihood of a clinically important difference between intravitreal ranibizumab and saline on the rate of vitrectomy by 16 weeks in eyes with vitreous hemorrhage from PDR. For both treatment groups, the vitrectomy rates were lower than expected based on previous studies which enrolled eyes with longer vitreous hemorrhage duration. Secondary outcomes such as change in visual acuity, completion of PRP, and frequency of recurrent vitreous hemorrhage suggest biologic activity and perhaps faster hemorrhage clearing with intravitreal ranibizumab. This study reports short term findings; long term benefits of either of these intravitreal regimens remain unknown.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix 1

Diabetic Retinopathy Clinical Research Network Clinical Sites that participated on this protocol

Sites are listed in order by number of subjects enrolled into the study. The number of subjects enrolled is noted in parenthesis preceded by the site location and the site name.

Personnel are listed as (I) for Study Investigator, (C) for Coordinator, (V) for Visual Acuity Tester, (P) for Photographer.

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References

1. Kempen JH, O'Colmain BJ, Leske MC, et al. The prevalence of diabetic retinopathy among adults in the United States. *Arch Ophthalmol*. 2004; 122:552–563. [PubMed: 15078674]
2. Flynn HJ, Chew E, Simons B, et al. Pars plana vitrectomy in the early treatment diabetic retinopathy study: ETDRS report number 17. *Ophthalmology*. 1992; 99:1351–1357. [PubMed: 1407968]
3. American Society of Retina Specialist. PAT Survey. 2008
4. Smiddy WE, Flynn HW Jr. Vitrectomy in the management of diabetic retinopathy. *Surv Ophthalmol*. 1999; 43:491–507. [PubMed: 10416792]
5. Yanoff, M.; Duker, JS. *Ophthalmology*. 3rd ed.. Vitrectomy: Mosby Elsevier; 1999.
6. Adamis AP, Miller JW, Bernal MT, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol*. 1994; 118:445–450. [PubMed: 7943121]
7. Adamis AP, Shima DT, Tolentino MJ, et al. Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris neovascularization in a nonhuman primate. *Arch Ophthalmol*. 1996; 114.
8. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med*. 1994; 331:1480–1487. [PubMed: 7526212]
9. Aiello LP, Pierce EA, Foley ED, et al. Suppression of retinal neovascularization in vivo by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF-receptor chimeric proteins. *Proc Natl Acad Sci USA*. 1995; 92:10457–10461. [PubMed: 7479819]
10. Amano S, Rohan R, Kuroki M, et al. Requirement for vascular endothelial growth factor in wound- and inflammation-related corneal neovascularization. *Invest Ophthalmol Vis Sci*. 1998; 39:18–22. [PubMed: 9430540]
11. Krzystolik MG, Afshari MA, Adamis AP, et al. Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment. *Arch Ophthalmol*. 2002; 120:338–346. [PubMed: 11879138]
12. Malecaze F, Clamens S, Simorre-Pinatel V, et al. Detection of vascular endothelial growth factor messenger RNA and vascular endothelial growth factor-like activity in proliferative diabetic retinopathy. *Arch Ophthalmol*. 1994; 112:1476–1482. [PubMed: 7980139]

13. Schwesinger C, Yee C, Rohan RM, et al. Intrachoroidal neovascularization in transgenic mice overexpressing vascular endothelial growth factor in the retinal pigment epithelium. *Am J Pathol.* 2001; 158:1161–1172. [PubMed: 11238064]
14. Tolentino MJ, Miller JW, Gragoudas ES, et al. Vascular endothelial growth factor is sufficient to produce iris neovascularization and neovascular glaucoma in a nonhuman primate. *Arch Ophthalmol.* 1996; 114:964–970. [PubMed: 8694732]
15. Aiello LP, Bursell SE, Clermont A, et al. Vascular endothelial growth factor-induced retinal permeability is mediated by protein kinase C in vivo and suppressed by an orally effective beta-isoform-selective inhibitor. *Diabetes.* 1997; 46:1473–1480. [PubMed: 9287049]
16. Tolentino MJ, McLeod DS, Taomoto M, et al. Pathologic features of vascular endothelial growth factor-induced retinopathy in the nonhuman primate. *Am J Ophthalmol.* 2002; 133:373–385. [PubMed: 11860975]
17. Tolentino MJ, Miller JW, Gragoudas ES, et al. Intravitreal injections of vascular endothelial growth factor produce retinal ischemia and microangiopathy in an adult primate. *Ophthalmology.* 1996; 103:1820–1828. [PubMed: 8942877]
18. Spaide RF, Fisher YL. Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage. *Retina.* 2006; 26:275–278. [PubMed: 16508426]
19. Kuppermann BD, Thomas EL, de Smet MD, et al. Pooled efficacy results from two multinational randomized controlled clinical trials of a single intravitreal injection of highly purified ovine hyaluronidase (Vitrace) for the management of vitreous hemorrhage. *Am J Ophthalmol.* 2005; 140:573–584. [PubMed: 16125661]
20. Li G, Shih WJ, Xie T, et al. A sample size adjustment procedure for clinical trials based on conditional power. *Biostatistics.* 2002; 3:277–287. [PubMed: 12933618]
21. Hosmer, D.; Lemeshow, S. *Wiley Series in Probability and Statistics.* New York: 1999. *Applied survival analysis: regression modeling of time to event data.*
22. Lee EW, Wei LJ, Amato DA. *Cox-type regression analysis for large numbers of small groups of correlated failure time observations* Dordrecht: Kluwer Academic. 1992
23. Verbeke, G.; Molenberghs, G. *Springer Series in Statistics.* New York: Springer; 2000. *Linear mixed models for longitudinal data.*
24. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ.* 1994; 308:81–106. [PubMed: 8298418]
25. Huang YH, Yeh PT, Chen MS, et al. Intravitreal bevacizumab and panretinal photocoagulation for proliferative diabetic retinopathy associated with vitreous hemorrhage. *Retina.* 2009; 29:1134–1140. [PubMed: 19672218]
26. Arevalo JF, Wu L, Sanchez JG, et al. Intravitreal bevacizumab (Avastin) for proliferative diabetic retinopathy: 6-months follow-up. *Eye.* 2009; 23:117–123. [PubMed: 17891058]
27. Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology.* 2010; 117:1064–77. e35. [PubMed: 20427088]
28. The Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating short-term effects of intravitreal ranibizumab or triamcinolone acetonide on macular edema following focal/grid laser for diabetic macular edema in eyes also receiving panretinal photocoagulation. *Retina.* 2011; 31:1009–1027. [PubMed: 21394052]
29. Arevalo JF, Maia M, Flynn HW Jr, et al. Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. *Br J Ophthalmol.* 2008; 92:213–216. [PubMed: 17965108]
30. Liu L, Wu WC, Yeung L, et al. Ghost cell glaucoma after intravitreal bevacizumab for postoperative vitreous hemorrhage following vitrectomy for proliferative diabetic retinopathy. *Ophthalmic Surg Lasers Imaging.* 2010; 41:72–77. [PubMed: 20128573]

Figure 1.

Cumulative Probability of Vitrectomy Surgery by 16 Weeks of Study Follow-up.

Categorization of events and censoring into intervals was defined by visit date if the visit occurred, otherwise using the target date of the visit.

*Number of eyes with follow up data at the start of the interval, and no vitrectomy prior to the start of the interval.

** Number of eyes with vitrectomy during the subsequent 4-week period.

Figure 2.

Cumulative Probability of Complete PRP by 16 Weeks of Study Follow-up. Categorization of events and censoring into intervals was defined by visit date if the visit occurred, otherwise using the target date of the visit. Complete PRP was defined as 500 μ m size burns on the retina placed no further than 1 to 2 burns widths apart beginning $\sim$ 3000 μ m from the macular center and extending to the equator for 12 clock hours (or at least 10 clock hours if vitreous hemorrhage precluded sufficient treatment or evaluation of all 12 clock hours).

*Number of eyes with follow up data at the start of the interval, and with no complete PRP prior to the start of the interval.

** Number of eyes with complete PRP during the subsequent 4-week period.

Table 1**Baseline Study Participant and Ocular Characteristics**

	Ranibizumab Injection N =125	Saline Injection N =136
Subject Characteristics		
Gender: Women	65 (52%)	70 (51%)
Age (years)		
Median (25 th , 75 th percentile)	61 (50, 67)	58 (49, 64)
Mean $\pm$ standard deviation	60 (12)	57 (12)
Race, no. (%)		
White	67 (54%)	70 (51%)
African-American	20 (16%)	22 (16%)
Hispanic or Latino	32 (26%)	34 (25%)
Asian	1 (<1%)	4 (3%)
Native Hawaiian/Other Pacific Islander	2 (2%)	1 (<1%)
American Indian/Alaskan Native	0	1 (<1%)
More than one race	2 (2%)	1 (<1%)
Unknown / not reported	1 (<1%)	2 (1%)
Diabetes Type, no. (%)		
Type 1	21 (17%)	31 (23%)
Type 2	101 (81%)	99 (73%)
Uncertain	3 (2%)	6 (4%)
Duration of Diabetes (years) - Median (25th, 75th percentile)	19 (12, 28)	21 (16, 27)
HbA1c (%)		
Median (25 th , 75 th percentile)	7.7 (6.7, 8.7)	8.0 (6.9, 9.3)
Mean $\pm$ standard deviation	7.8 (1.6)	8.3 (1.7)
Pre-existing cardiovascular condition, no. (%)	44 (35%)	60 (44%)
Pre-existing hypertension, no. (%)	105 (84%)	117 (86%)
Prior PRP, no. (%)	62 (50%)	78 (57%)
Prior treatment for DME, no. (%)	53 (42%)	57 (42%)
Prior treatment with Anti-VEGF drug for DME, no. (%)	10 (8%)	18 (13%)
Lens Status (clinical exam), no. (%)		
Phakic	97 (78%)	98 (72%)
PC IOL	28 (22%)	38 (28%)
OCT signal strength, no. (%)		
= 0	74 (59%)	96 (71%)
> 0	50 (40%)	38 (28%)
Ultrasound completed to assess eligibility, no. (%)	62 (50%)	62 (46%)
Duration of vitreous hemorrhage since first documented on clinical exam, no. (%)		
<1 month	66 (53%)	75 (55%)
1–3 months	41 (33%)	39 (29%)

	Ranibizumab Injection N =125	Saline Injection N =136
4-6 months	7 (6%)	11 (8%)
>6 months	11 (9%)	11 (8%)
E-ETDRS Visual Acuity (letter score)		
Median (25th, 75th percentile)	34 (0, 61)	28 (0, 59)
Snellen equivalent	20/200	20/320
Mean $\pm$ standard deviation	34 (29)	32 (29)
Snellen equivalent	20/200	20/250
E-ETDRS Visual Acuity (Snellen equivalent), no. (%)		
69 letter score - (20/40 or better)	20 (16%)	21 (15%)
68 to 49 letter score - (20/50 to 20/100)	32 (26%)	19 (14%)
48 to 24 letter score - (20/125 to 20/320)	18 (14%)	37 (27%)
23 to 1 letter score - (20/400 to 20/800-3)	19 (15%)	18 (13%)
0 letter score – counting fingers	12 (10%)	15 (11%)
0 letter score – hand motion	19 (15%)	20 (15%)
0 letter score – light perception	5 (4%)	6 (4%)
0 letter score –no light perception	0	0
IOP, no. (%)		
Median (25th, 75th percentile)	15 (12, 17)	14 (12, 17)
Mean $\pm$ standard deviation	15 (3)	14 (3)
Anti-platelet aggregation and anti-coagulant drugs[*], no. (%)		
Aspirin	50 (55%)	57 (58%)
Other anti-platelet aggregation drugs	19 (21%)	21 (21%)
Anti-coagulants	7 (8%)	6 (6%)
NSAIDs	15 (17%)	15 (15%)

DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; VEGF = vascular endothelial growth factor; IOP = intraocular pressure;; NPDR = non-proliferative diabetic retinopathy; PRP = panretinal photocoagulation; PDR = proliferative diabetic retinopathy.

^{*} Reported at any time during the study.

Table 2
Visual Acuity Letter Score (approximate Snellen equivalent) at Follow-Up Visits

	N	Ranibizumab Injection	N	Saline Injection	p-value*
Baseline	125		136		
Median (25 th , 75 th percentile)		34 (0, 61)		28 (0, 59)	-
Snellen Equivalent		20/200 (<20/800, 20/63)		20/320 (<20/800, 20/63)	
Mean ± standard deviation		34 (20/200) ± 29		32 (20/250) ± 29	
4 Weeks	122		128		
Median (25 th , 75 th percentile)		56 (16, 70)		45 (4, 72)	
Snellen Equivalent		20/80 (20/500, 20/40)		20/125 (20/800, 20/40)	0.67
Mean ± standard deviation		45(20/125) ± 30		42 (20/160) ± 31	
Mean Change ± standard deviation		11 ± 19		10 ± 24	
8 Weeks	121		127		
Median (25 th , 75 th percentile)		61 (29, 76)		54 (19, 74)	0.14
Snellen Equivalent		20/63 (20/250, 20/32)		20/80 (20/400, 20/32)	
Mean ± standard deviation		51 (20/100) ± 30		47 (20/125) ± 31	
Mean Change ± standard deviation		17 ± 24		14 ± 28	
12 Weeks	119		129		
Median (25 th , 75 th percentile)		68 (48, 78)		60 (27, 73)	0.04
Snellen Equivalent		20/50 (20/125, 20/32)		20/63 (20/320, 20/40)	
Mean ± standard deviation		57 (20/80) ± 27		49 (20/100) ± 29	
Mean Change ± standard deviation		22 ± 23		16 ± 31	

* N represents the number of eyes. Treatment comparisons were performed using a mixed model adjusting for visual acuity.

Table 3

Visual Acuity Binary Outcomes at Follow-Up Visits.

	N	Ranibizumab Injection	N	Saline Injection	p- value*
Baseline	125		136		
VA better than 69 letter score (20/40 or better)		20 (16%)		21 (15%)	
Severe VA deficiency – <38 letter score (<20/200)		62 (50%)		71 (52%)	-
Very severe VA deficiency – <4 letter score (<20/800)		38 (30%)		43 (32%)	
4 Weeks	122		129		
VA better than 69 letter score (20/40 or better) and no vitrectomy prior to visit		35 (29%)		38 (29%)	0.72
Severe VA deficiency – <38 letter score (<20/200)		46 (38%)		49 (38%)	0.65
Very severe VA deficiency - <4 letter score (<20/800)		25 (20%)		32 (25%)	0.43
8 Weeks	121		127		
VA better than 69 letter score (20/40 or better) and no vitrectomy prior to visit		43 (36%)		42 (33%)	0.80
Severe VA deficiency – <38 letter score (<20/200)		36 (30%)		44 (35%)	0.51
Very severe VA deficiency – <4 letter score (<20/800)		19 (16%)		24 (19%)	0.55
12 Weeks	119		129		
VA better than 69 letter score (20/40 or better) and no vitrectomy prior to visit		53 (45%)		43 (33%)	0.08
Severe VA deficiency – <38 letter score (<20/200)		24 (20%)		35 (27%)	0.23
Very severe VA deficiency – <4 letter score (<20/800)		13 (11%)		21 (16%)	0.27

* Treatment comparisons were performed using a logistic regression model adjusting for baseline visual acuity

Table 4
OCT Signal Strength Binary Composite Outcome - Among Participants with Baseline OCT Signal Strength = 0

	N [‡]	Ramizumab Injection	N	Saline Injection	p-value*
Baseline	125		136		
OCT Signal Strength > 0		50 (40%)		38 (28%)	-
OCT Signal Strength = 0		74 (59%)		96 (71%)	
Among Participants with Baseline OCT Signal Strength = 0					
4 Weeks	71		89		
OCT Signal Strength > 0 and no vitrectomy		26 (37%)		27 (30%)	0.50
OCT Signal Strength = 0 or vitrectomy		44 (63%)		62 (70%)	
8 Weeks	69		87		
OCT Signal Strength > 0 and no vitrectomy		32 (46%)		33 (38%)	0.33
OCT Signal Strength = 0 or vitrectomy		37 (54%)		54 (62%)	
12 Weeks	66		88		
OCT Signal Strength > 0 and no vitrectomy		34 (51%)		46 (52%)	0.87
OCT Signal Strength = 0 or vitrectomy		32 (49%)		42 (48%)	

* Treatment comparisons were performed using the Fisher's Exact Test.

[‡] N represents the number of eyes.

Table 5**Major Ocular Adverse Events during Follow-Up**

	Ranibizumab Injection *	Saline Injection *
<i>Up to 16 weeks of Study Follow-Up</i>	N=125	N=136
Endophthalmitis	0	1 (<1%)
Traction and/or rhegmatogenous retinal detachment on clinical exam	6 (5%)	5 (4%)
Traction and/or rhegmatogenous retinal detachment on ultrasound	0	3 (2%)
Retinal detachment on AE form	9 (7%)	7 (5%)
Traction and/or rhegmatogenous retinal detachment on any of the 3 above	10 (8%)	11 (8%)
Angle or iris neovascularization	1 (<1%)	4 (3%)
Neovascular glaucoma	1 (<1%)	1 (<1%)
Cataract Surgery	0	2 (1%)
Recurrent vitreous hemorrhage on clinical exam [‡]	8 (6%)	23 (17%)
Elevated Intraocular Pressure/Glaucoma	16 (13%)	19 (14%)
Increase of IOP 10 mm Hg from baseline	8 (6%)	11 (8%)
IOP 30 mm Hg	4 (3%)	4 (3%)
Currently on IOP-lowering medication, but not at baseline	13 (10%)	14 (10%)
Glaucoma surgery at anytime	0	0

* Percentages are based on the number of eyes.

[‡] Treatment comparison for recurrent vitreous hemorrhage was performed using Fisher Exact test (p-value = 0.01)