Clinical Trials in Diabetic Retinopathy

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1. Laser Trials

(1) Diabetic Retinopathy Study (DRS)

The Diabetic Retinopathy Study Research Group: Photocoagulation treatment of proliferative diabetic retinopathy: Clinical Application of Diabetic Retinopathy Study (DRS) Findings: DRS Report No. 8. Ophthalmology 88: 583-600, 1981.

The Diabetic Retinopathy Study Research Group: Four risk factors for severe visual loss in diabetic retinopathy: DRS Report No. 3. Arch Ophthalmol 97: 654-655, 1979.

- The DRS was a randomized, prospective clinical trial evaluating photocoagulation (PDR) treatment to one eye of patients with clear media and advanced NPDR or PDR in both eyes. The primary outcome measurement in the DRS was severe visual loss (SVL) defined as a visual acuity of less than 5/200 on two consecutive follow-up examinations four months apart.

- The DRS demonstrated a 50% or greater reduction in the rates of SVL in eyes treated with PRP compared to untreated control eyes during follow up of up to 5 years.

- DRS "high-risk" PDR was defined as any one of the following:
  - Mild (1/4 to 1/3 disc area) neovascularization of the disc (NVD) with vitreous hemorrhage.
  - Moderate to severe NVD with or without vitreous hemorrhage.
  - Moderate (1/2 disc area) neovascularization elsewhere (NVE) with vitreous hemorrhage

- Another way of defining DRS "high-risk PDR is by any three of the four Retinopathy Risk Factors:
  - The presence of vitreous or preretinal hemorrhage.
  - The presence of new vessels.
  - Location of new vessels on or near the optic disc.
  - Moderate to severe extent of new vessels.

- The DRS recommended prompt PRP of eyes with high-risk PDR because this group had the highest risk of SVL. The complications of argon laser PRP in the DRS were generally mild but included a drop in visual acuity of one or more lines in 11% and visual field loss in 5%.

(2) The Early Treatment Diabetic Retinopathy Study (ETDRS)

The Early Treatment Diabetic Retinopathy Study Research Group: Photocoagulation for diabetic macular edema. Arch Ophthalmol 103: 1796-1806, 1985.

The Early Treatment Diabetic Retinopathy Study Research Group: Early Photocoagulation for diabetic retinopathy. ETDRS Report No. 9. Ophthalmology (Suppl) 98: 766-785, 1991.

The Early Treatment Diabetic Retinopathy Study Research Group: Effects of Aspirin Treatment on Diabetic Retinopathy. ETDRS Report No. 20. Arch Ophthalmol 113: 52-55, 1995.

Flynn HW JR., Chew EY, Simons BD, et al. Pars plana vitrectomy in the Early Treatment Diabetic Retinopathy Study. ETDRS Report No. 17. Ophthalmology 99: 1351-1357, 1992.

- The ETDRS was a randomized, prospective study evaluating photocoagulation and aspirin treatment of diabetic patients with less than high-risk PDR in both eyes. The primary outcome measurement in the ETDRS was moderate visual loss (MVL) comparing baseline with follow up visual acuities. MLV was defines as a doubling of the visual angle (e.g., a drop from 20/20 to 20/40 or from 20/50 to 20/100), a drop of 15 or more letters on ETDRS visual acuity charts, or a drop of 3 or more lines of Snellen equivalent.

- It defined clinically significant macular edema (CSME) as any one of the following:

    - Retinal edema located at or within 500 µm of the center of the macula.
    - Hard exudates at or within 500µm of the center if associated with thickening of adjacent retina.
    - A zone of thickening larger than one disc area if located within 1 disc diameter of the center of the macula.

- Classification of diabetic retinopathy
    - Non-proliferative Diabetic Retinopathy (NPDR)
        - **Mild -** At least one: Microaneurysms or Dot/blot hemorrhages
        - **Moderate –** Marked hemorrhages/microaneurysms or Cotton wool spots (CWS) or Venous beading (VB) not fulfilling the 4-2-1 rule.
        - **Severe/Very Severe – as per 4-2-1 Rule: –**
            - Marked hemorrhages/microaneurysms in all **4** quadrants
            - VB in **2** or more quadrants or
            - IRMA's in **1** quadrant

          Severe - if 1 of the above 3 features present

          Very Severe - if 2 of the above 3 features present
    - Proliferative Diabetic Retinopathy (PDR) – Including high-risk

- The ETDRS addresses three issues:

  - 1) The efficacy of laser treatment for macular edema. It showed a 50% or greater reduction in the rates of MVL in laser treated eyes with CSME (compared to untreated control eyes)
  - 2) The timing for initiating PRP. The ETDRS stated that provided follow up can be maintained, scatter panretinal photocoagulation was not recommended for eyes with mild or moderate NPDR. When NPDR becomes more severe and approaches the high-risk stage, scatter PRP treatment can be considered and usually should not be delayed when the retinopathy reaches the high-risk stage.
  - 3) The value of aspirin treatment. At a dosage of 650mg per day, aspirin did not alter the rates of progression of diabetic retinopathy, had no influence on visual acuity outcomes, and did not increase the risk of vitreous hemorrhage. Therefore at this dosage, there appears to be no ocular contraindication to the use of aspirin in persons with diabetes who require it for treatment of cardiovascular diseases or for other medical indications.

- Vitrectomy in the ETDRS was a secondary issue. Vitrectomy was performed in 208 (5.6%) of the 3711 patients (243 eyes) enrolled in the ETDRS. The 5-year vitrectomy rates in the ETDRS were 5.4% in patients assigned to aspirin and 5.2% in patients assigned the placebo. For eyes with more severe retinopathy and macular edema, the 5-year rate for the combined endpoint of severe visual loss or occurrence of vitrectomy was higher (10.3%) in eyes assigned to deferral of photocoagulation unless HRC developed and was lower (5.6%) in full scatter treated eyes to 6.9% in mild scatter treated eyes) in the groups assigned to early PRP treatment.

(3) DRCR (Protocol A)

Comparison of the Modified Early Treatment Diabetic Retinopathy Study and Mild Macular Grid Laser Photocoagulation Strategies for Diabetic Macular Edema

Writing Committee for the Diabetic Retinopathy Clinical Research Network

Objective: To compare 2 laser photocoagulation techniques for treatment of diabetic macular edema: the modified Early Treatment Diabetic Retinopathy Study (ETDRS) direct/grid photocoagulation technique and a potentially milder (but potentially more extensive) mild macular grid (MMG) laser technique in which micro aneurysms are not treated directly and small mild burns are placed throughout the macula, whether or not edema is present.

Methods: Two hundred sixty-three subjects (mean age, 59 years) with previously untreated diabetic macular edema were randomly assigned to receive laser photocoagulation by either the modified ETDRS (162 eyes) or MMG (161 eyes) technique. Visual acuity, fundus photographs, and optical coherence tomography measurements were obtained at baseline and at 3.5, 8, and 12 months. Treatment was repeated if diabetic macular edema persisted.

Main Outcome Measure: Change in optical coherence tomography measurements at 12-month follow-up.

Results: Among eyes with a baseline central subfield thickness of 250 μm or greater, central subfield thickening decreased by an average of 88 μm in the modified ETDRS group and by 49 μm in the MMG group at 12-month follow-up (adjusted mean difference, 33 μm; 95% confidence interval, 5-61 μm; P=.02). Weighted inner zone thickening by optical coherence tomography decreased by 42 μm in the modified ETDRS group and by 28 μm in the

MMG group (adjusted mean difference, 14 μm; 95% confidence interval, 1-27 μm; P=.04); maximum retinal thickening (maximum thickening of the central and 4 inner sub- fields) decreased by 66 and 39 μm, respectively (adjusted mean difference, 27 μm; 95% confidence interval, 6-47 μm; P=.01), and retinal volume decreased by 0.8 and 0.4 mm^3, respectively (adjusted mean difference, 0.3 mm^3; 95% confidence interval, 0.02-0.53 mm^3; P=.03). At 12 months, the mean change in visual acuity was 0 letters in the modified ETDRS group and 2 letters worse in the MMG group (adjusted mean difference, 2 letters; 95% confidence interval, −0.5 to 5 letters; P=.10).

Conclusions: At 12 months after treatment, the MMG technique was less effective at reducing optical coherence tomography–measured retinal thickening than the more extensively evaluated current modified ETDRS laser photocoagulation approach. However, the visual acuity outcome with both approaches is not substantially different. Given these findings, a larger long-term trial of the MMG technique is not justified.

Application to Clinical Practice: Modified ETDRS focal photocoagulation should continue to be a standard approach for treating diabetic macular edema.

Trial Registration: clinicaltrials.gov Identifier: NCT00071773.

Arch Ophthalmol. 2007;125:469-480

(4) DRCR (Protocol B)

A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Focal/Grid Photocoagulation for Diabetic Macular Edema

Diabetic Retinopathy Clinical Research Network

Objective: To evaluate the efficacy and safety of 1-mg and 4-mg doses of preservative-free intravitreal triamcinolone in comparison with focal/grid photocoagulation for the treatment of diabetic macular edema (DME).

Design: Multicenter, randomized clinical trial.

Participants: Eight hundred forty study eyes of 693 subjects with DME involving the fovea and with visual acuity of 20/40 to 20/320.

Methods: Eyes were randomized to focal/grid photocoagulation (n = 330), 1 mg intravitreal triamcinolone (n = 256), or 4 mg intravitreal triamcinolone (n = 254). Retreatment was given for persistent or new edema at 4-month intervals. The primary outcome was evaluated at 2 years.

Main Outcome Measures: Visual acuity measured with the electronic Early Treatment Diabetic Retinopathy Study method (primary), optical coherence tomography-measured retinal thickness (secondary), and safety.

Results: At 4 months, mean visual acuity was better in the 4-mg triamcinolone group than in either the laser group ($P<0.001$) or the 1-mg triamcinolone group ($P = 0.001$). By 1 year, there were no significant differences among groups in mean visual acuity. At the 16-month visit and extending through the primary outcome visit at 2 years, mean visual acuity was better in the laser group than in the other 2 groups (at 2 years, $P = 0.02$ comparing the laser and 1-mg groups, $P = 0.002$ comparing the laser and 4-mg groups, and $P = 0.49$ comparing the 1-mg and 4-mg groups). Treatment group differences in the visual acuity outcome could not be attributed solely to cataract formation. Optical coherence tomography results generally paralleled the visual acuity results. Intraocular pressure increased from baseline by 10 mmHg or more at any visit in 4%, 16%, and 33% of eyes in the 3 treatment groups, respectively, and cataract surgery was performed in 13%, 23%, and 51% of eyes in the 3 treatment groups, respectively.

Conclusions: Over a 2-year period, focal/grid photocoagulation is more effective and has fewer side effects than 1-mg or 4-mg doses of preservative-free intravitreal triamcinolone for most patients with DME who have characteristics similar to the cohort in this clinical trial. The results of this study also support that focal/grid photocoagulation currently should be the benchmark against which other treatments are compared in clinical trials of DME.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2008;115:1447–1459

(5) DRCR (Protocol F)

Observational Study of the Development of Diabetic Macular Edema Following Panretinal (Scatter) Photocoagulation Given in 1 or 4 Sittings

*Diabetic Retinopathy Clinical Research Network**

Objective: To compare the effects of single-sitting vs 4-sitting panretinal photocoagulation (PRP) on macular edema in subjects with severe nonproliferative or early proliferative diabetic retinopathy with relatively good visual acuity and no or mild center-involved macular edema.

Methods: Subjects were treated with 1 sitting or 4 sittings of PRP in a nonrandomized, prospective, multicentered clinical trial.

Main Outcome Measure: Central subfield thickness on optical coherence tomography (OCT).

Results: Central subfield thickness was slightly greater in the 1-sitting group (n=84) than in the 4-sitting group (n=71) at the 3-day (*P*=.01) and 4-week visits (*P*=.003). At the 34-week primary outcome visit, the slight differences had reversed, with the thickness being slightly greater in the 4-sitting group than in the 1-sitting group (*P*=.06). Visual acuity differences paralleled OCT differences.

Conclusions: Our results suggest that clinically meaningful differences are unlikely in OCT thickness or visual acuity following application of PRP in 1 sitting compared with 4 sittings in subjects in this cohort. More definitive results would require a large randomized trial.

Application to Clinical Practice: These results suggest PRP costs to some patients in terms of travel and lost productivity as well as to eye care providers could be reduced.

Trial Registration: clinicaltrials.gov Identifier: NCT00687154.

Arch Ophthalmol. 2009;127(2):132-140

(6) DRCR (Protocol K)

Retina. 2009 ; 29(10): 1436–1443.

The Course of Response to Focal/ Grid Photocoagulation for Diabetic Macular Edema

The Diabetic Retinopathy Clinical Research Network

Abstract

Purpose—To determine whether eyes with center involved diabetic macular edema (DME), treated with focal/grid photocoagulation, in which there is a reduction in central subfield thickness (CST) measured with optical coherence tomography (OCT) after 16 weeks, will continue to improve if retreatment is deferred.

Methods—Prospective, multi-center, observational, single group focal/grid photocoagulation study of 122 eyes with center involved DME (OCT CST ≥250μ). At the 16-week visit and continuing every 8 weeks, eyes were assessed for retreatment and additional laser was deferred if the visual acuity letter score improved ≥5 letters or OCT CST decreased ≥10% compared with the visit 16 weeks prior.

Results—Of the 115 eyes that completed the 16-week visit, 54 (47%) had a decrease in CST by ≥10% compared with baseline. Of these, 26 (48%) had a CST ≥250μ at 16 weeks and were evaluable at 32 weeks. Eleven (42%, 95% confidence interval 23% to 63%) of the 26 eyes had a further decrease in CST ≥10% from 16 to 32 weeks without further treatment.

Conclusion—Sixteen weeks following focal/grid laser for DME, in eyes with a definite reduction, but not resolution, of central edema, 23% to 63% will continue to improve without additional treatment.

(7) DRCR (Protocol V)

Comparative Effectiveness Study of Laser, Observation and Aflibercept for DME in eyes with Very Good VA. (NCT01909791)

Official Title: Treatment for Central-Involved Diabetic Macular Edema in Eyes With Very Good Visual Acuity.

Study Type: Interventional/Randomized/Safety - Efficacy Study / Parallel Assignment / Single Blind (Outcomes Assessor) Masking

Primary Objective - To compare the % of eyes that have lost at least 5 letters of visual acuity at 2 years compared with baseline mean visual acuity in eyes with central-involved DME and good visual acuity defined as a Snellen equivalent of 20/25 or better (electronic-ETDRS letter score of 79 or better) that receive

(1) Prompt focal/grid photocoagulation + deferred anti-VEGF,

(2) Observation + deferred anti-VEGF, or

(3) Prompt anti-VEGF

Secondary Objective - Other visual acuity outcomes

- Percentage of eyes needing anti-VEGF treatment
- Optical Coherence Tomography (OCT) Outcomes
- Proportion of eyes avoiding vitreous hemorrhage or panretinal photocoagulation (PRP) or vitrectomy for PDR
- Safety Outcomes
- Associated treatment and follow-up exam costs

Current Status – Recruiting participants

Estimated Completion Date – March 2017

(8) CLARITY Trial

Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial

Sobha Sivaprasad, A Toby Prevost, Joana C Vasconcelos, Amy Riddell, Caroline Murphy, Joanna Kelly, James Bainbridge, Rhiannon Tudor-Edwards, David Hopkins, Philip Hykin, on behalf of the CLARITY Study Group*

Summary

Background Proliferative diabetic retinopathy is the most common cause of severe sight impairment in people with diabetes. Proliferative diabetic retinopathy has been managed by panretinal laser photocoagulation (PRP) for the past 40 years. We report the 1 year safety and efficacy of intravitreal aflibercept.

Methods In this phase 2b, single-blind, non-inferiority trial (CLARITY), adults (aged ≥18 years) with type 1 or 2 diabetes and previously untreated or post-laser treated active proliferative diabetic retinopathy were recruited from 22 UK ophthalmic centres. Patients were randomly assigned (1:1) to repeated intravitreal aflibercept (2 mg/0·05 mL at baseline, 4 weeks, and 8 weeks, and from week 12 patients were reviewed every 4 weeks and aflibercept injections were given as needed) or PRP standard care (single spot or mutlispot laser at baseline, fractionated fortnightly thereafter, and from week 12 patients were assessed every 8 weeks and treated with PRP as needed) for 52 weeks. Randomisation was by minimisation with a web-based computer generated system. Primary outcome assessors were masked optometrists. The treating ophthalmologists and participants were not masked. The primary outcome was defined as a change in best-corrected visual acuity at 52 weeks with a linear mixed-effect model that estimated adjusted treatment effects at both 12 weeks and 52 weeks, having excluded fluctuations in best corrected visual acuity owing to vitreous haemorrhage. This modified intention-to-treat analysis was reapplied to the per protocol participants. The non-inferiority margin was prespecified as −5 Early Treatment Diabetic Retinopathy Study letters. Safety was assessed in all participants. This trial is registered with ISRCTN registry, number 32207582.

Findings We recruited 232 participants (116 per group) between Aug 22, 2014 and Nov 30, 2015. 221 participants (112 in aflibercept group, 109 in PRP group) contributed to the modified intention-to-treat model, and 210 participants (104 in aflibercept group and 106 in PRP group) within per protocol. Aflibercept was non-inferior and superior to PRP in both the modified intention-to-treat population (mean best corrected visual acuity difference 3·9 letters [95% CI 2·3–5·6], p<0·0001) and the per-protocol population (4·0 letters [2·4–5·7], p<0·0001). There were no safety concerns. The 95% CI adjusted difference between groups was more than the prespecified acceptable margin of −5 letters at both 12 weeks and 52 weeks.

Interpretation Patients with proliferative diabetic retinopathy who were treated with intravitreal aflibercept had an improved outcome at 1 year compared with those treated with PRP standard care.

II. Pharmacotherapy Trials

(1) DRCR Protocol I

Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema

*The Diabetic Retinopathy Clinical Research Network**
*Writing Committee: Michael J. Elman, MD; Lloyd Paul Aiello, MD, PhD; Roy W. Beck, MD, PhD; Neil M. Bressler, MD; Susan B. Bressler, MD; Allison R. Edwards, MS; Frederick L. Ferris III, MD; Scott M. Friedman, MD; Adam R. Glassman, MS; Kellee M. Miller, MPH; Ingrid U. Scott, MD, MPH; Cynthia R. Stockdale, MSPH; Jennifer K. Sun, MD, MPH. *The members of the DRCR Network who participated in this protocol are listed in Appendix 5.*

Objective: Evaluate intravitreal 0.5 mg ranibizumab or 4 mg triamcinolone combined with focal/grid laser compared with focal/grid laser alone for treatment of diabetic macular edema (DME).

Design: Multicenter, randomized clinical trial.

Participants: A total of 854 study eyes of 691 participants with visual acuity (approximate Snellen equivalent) of 20/32 to 20/320 and DME involving the fovea.

Methods: Eyes were randomized to sham injection + prompt laser (n=293), 0.5 mg ranibizumab + prompt laser (n=187), 0.5 mg ranibizumab + deferred (≥24 weeks) laser (n=188), or 4 mg triamcinolone + prompt laser (n=186). Retreatment followed an algorithm facilitated by a web-based, real-time data-entry system.

Main Outcome Measures: Best-corrected visual acuity and safety at 1 year.

Results: The 1-year mean change (±standard deviation) in the visual acuity letter score from baseline was significantly greater in the ranibizumab + prompt laser group (+9±11, $P<0.001$) and ranibizumab + deferred laser group (+9±12, $P<0.001$) but not in the triamcinolone + prompt laser group (+4±13, $P=0.31$) compared with the sham + prompt laser group (+3±13). Reduction in mean central subfield thickness in the triamcinolone + prompt laser group was similar to both ranibizumab groups and greater than in the sham + prompt laser group. In the subset of pseudophakic eyes at baseline (n=273), visual acuity improvement in the triamcinolone + prompt laser group appeared comparable to that in the ranibizumab groups. No systemic events attributable to study treatment were apparent. Three eyes (0.8%) had injection-related endophthalmitis in the ranibizumab groups, whereas elevated intraocular pressure and cataract surgery were more frequent in the triamcinolone + prompt laser group. Two-year visual acuity outcomes were similar to 1-year outcomes.

Conclusions: Intravitreal ranibizumab with prompt or deferred laser is more effective through at least 1 year compared with prompt laser alone for the treatment of DME involving the central macula. Ranibizumab as applied in this study, although uncommonly associated with endophthalmitis, should be considered for patients with DME and characteristics similar to those in this clinical trial. In pseudophakic eyes, intravitreal triamcinolone + prompt laser seems more effective than laser alone but frequently increases the risk of intraocular pressure elevation.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. *Ophthalmology 2010;117:1064–1077 © 2010 by the American Academy of Ophthalmology.*

(1) DRCR Protocol I (3 year Results)

Intravitreal Ranibizumab for Diabetic Macular Edema with Prompt versus Deferred Laser Treatment *Three-Year Randomized Trial Results*

Diabetic Retinopathy Clinical Research Network Writing Committee: Michael J. Elman, MD,[1] Haijing Qin, MS,[2] Lloyd Paul Aiello, MD,[3] Roy W. Beck, MD,[2] Neil M. Bressler, MD,[4] Frederick L. Ferris III, MD,[5] Adam R. Glassman, MS,[2] Raj K. Maturi, MD, PC,[6] Michele Melia, ScM[2]*

Objective: To report the 3-year follow-up results within a previously reported randomized trial evaluating prompt versus deferred (for >24 weeks) focal/grid laser treatment in eyes treated with intravitreal 0.5 mg ranibizumab for diabetic macular edema (DME).

Design: Multicenter, randomized clinical trial.

Participants: Three hundred sixty-one participants with visual acuity of 20/32 to 20/320 (approximate Snellen equivalent) and DME involving the fovea.

Methods: Ranibizumab every 4 weeks until no longer improving (with resumption if worsening) and random assignment to prompt or deferred (>24 weeks) focal/grid laser treatment.

Main Outcome Measures: Best-corrected visual acuity and safety at the 156-week (3-year) visit.

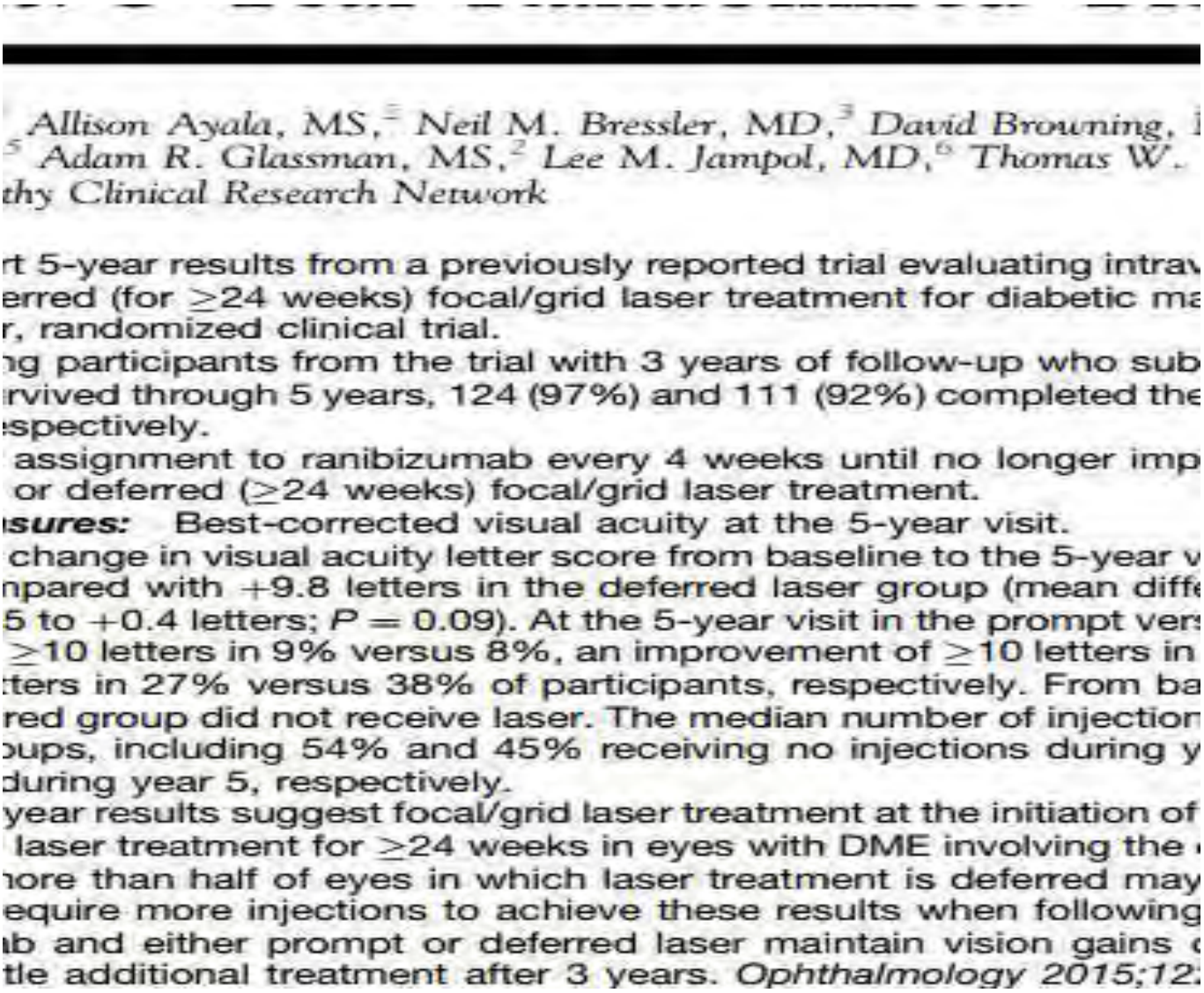
Results: The estimated mean change in visual acuity letter score from baseline through the 3-year visit was 2.9 letters more (9.7 vs. 6.8 letters; mean difference, 2.9 letters; 95% confidence interval, 0.4 –5.4 letters; P = 0.02) in the deferral group compared with the prompt laser treatment group. In the prompt laser treatment group and deferral group, respectively, the percentage of eyes with a >10-letter gain/loss was 42% and 56% (P = 0.02), whereas the respective percentage of eyes with a >10-letter gain/loss was 10% and 5% (P = 0.12). Up to the 3-year visit, the median numbers of injections were 12 and 15 in the prompt and deferral groups, respectively (P = 0.007), including 1 and 2 injections, respectively, from the 2-year up to the 3-year visit. At the 3-year visit, the percentages of eyes with central subfield thickness of 250 μm or more on time-domain optical coherence tomography were 36% in both groups (P = 0.90). In the deferral group, 54% did not receive laser treatment during the trial. Systemic adverse events seemed to be similar in the 2 groups.

Conclusions: These 3-year results suggest that focal/grid laser treatment at the initiation of intravitreal ranibizumab is no better, and possibly worse, for vision outcomes than deferring laser treatment for 24 weeks or more in eyes with DME involving the fovea and with vision impairment. Some of the observed differences in visual acuity at 3 years may be related to fewer cumulative ranibizumab injections during follow-up in the prompt laser treatment group. Follow-up through 5 years continues.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.

Ophthalmology 2012;119:2312–2318

(1) DRCR Protocol I (5 year Results)



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thy Clinical Research Network

rt 5-year results from a previously reported trial evaluating intrav
erred (for ≥24 weeks) focal/grid laser treatment for diabetic ma
r, randomized clinical trial.
ng participants from the trial with 3 years of follow-up who sub
rvived through 5 years, 124 (97%) and 111 (92%) completed the
spectively.
assignment to ranibizumab every 4 weeks until no longer imp
or deferred (≥24 weeks) focal/grid laser treatment.
sures: Best-corrected visual acuity at the 5-year visit.
change in visual acuity letter score from baseline to the 5-year v
npared with +9.8 letters in the deferred laser group (mean diffe
5 to +0.4 letters; $P = 0.09$). At the 5-year visit in the prompt vers
≥10 letters in 9% versus 8%, an improvement of ≥10 letters in
tters in 27% versus 38% of participants, respectively. From ba
red group did not receive laser. The median number of injection
oups, including 54% and 45% receiving no injections during y
during year 5, respectively.
year results suggest focal/grid laser treatment at the initiation of
laser treatment for ≥24 weeks in eyes with DME involving the
nore than half of eyes in which laser treatment is deferred may
equire more injections to achieve these results when following
ab and either prompt or deferred laser maintain vision gains
tle additional treatment after 3 years. *Ophthalmology 2015;12*

(2) DRCR (Ranibizumab +/- Laser in management of DME in vitrectomized versus non-vitrectomized eyes)

Ranibizumab Plus Prompt or Deferred Laser for Diabetic Macular Edema in Eyes with Vitrectomy Prior to Anti-Vascular Endothelial Growth Factor Therapy

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Background—The approach to managing diabetic macular edema (DME) in eyes with prior vitrectomy is based on limited evidence. Therefore, an exploratory post-hoc assessment of 3-year data from eyes with and without vitrectomy prior to randomization in a DRCR.net trial that evaluated ranibizumab+prompt or deferred laser for DME is presented.

Methods—Visual acuity (VA) and ocular coherence tomography (OCT) outcomes were compared between eyes with and without prior vitrectomy.

Results—At baseline eyes with prior vitrectomy (n = 25) had longer duration of diabetes, worse VA, less thickened central subfield measurements on OCT, and were more apt to have worse diabetic retinopathy severity level or prior treatment for macular edema or cataract surgery than eyes without a history of vitrectomy (n = 335). Analyses adjusted for these baseline imbalances did not identify substantial differences between eyes with and without prior vitrectomy at each annual visit through 3 years for the favorable VA, OCT central subfield thickness or volume outcomes, although OCT improvement appeared slower in vitrectomy eyes during the first year.

Conclusion—This study provides little evidence that the beneficial clinical outcomes for patients with center-involved DME treated with anti-VEGF are affected in the long term by prior vitrectomy.

(3) DRCR (Protocol N)

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

*Diabetic Retinopathy Clinical Research Network**

Importance: Vascular endothelial growth factor plays a role in proliferative diabetic retinopathy (PDR). Intravitreal injection of saline has been shown potentially to lead to improved visual acuity compared with observation alone in eyes with vitreous hemorrhage. Therefore, it is important to determine if intravitreal anti–vascular endothelial growth factor can reduce vitrectomy rates (and risks associated with vitrectomy) compared with saline for vitreous hemorrhage from PDR that precludes placement or confirmation of complete panretinal photocoagulation.

Objective: To evaluate intravitreal ranibizumab compared with intravitreal saline injections on vitrectomy rates for vitreous hemorrhage from PDR.

Design: Phase 3, double-masked, randomized, multicenter clinical trial. Data reported were collected from June 2010 to March 2012 and include 16 weeks of follow-up.

Setting: Community-based and academic-based ophthalmology practices specializing in retinal diseases.

Participants: Two hundred sixty-one eyes of 261 study participants, who were at least 18 years of age with type 1 or type 2 diabetes mellitus. Study eyes had vitreous hemorrhage from PDR precluding panretinal photocoagulation completion.

Intervention: Eyes were randomly assigned to 0.5-mg intravitreal ranibizumab (n=125) or intravitreal saline (n=136) at baseline and 4 and 8 weeks.

Main Outcome Measure: Cumulative probability of vitrectomy within 16 weeks.

Results: Cumulative probability of vitrectomy by 16 weeks was 12% with ranibizumab vs 17% with saline (difference, 4%; 95% CI, −4% to 13%) and of complete panretinal photocoagulation without vitrectomy by 16 weeks was 44% and 31%, respectively ($P=.05$). The mean (SD) visual acuity improvement from baseline to 12 weeks was 22 (23) letters and 16 (31) letters, respectively ($P=.04$). Recurrent vitreous hemorrhage occurred within 16 weeks in 6% and 17%, respectively ($P=.01$). One eye developed endophthalmitis after saline injection.

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

Trial Registration: The study is listed on www.clinicaltrials.gov, under identifier NCT00996437 (website registration date October 14, 2009).

JAMA Ophthalmol. 2013;131(3):283-293.
Published online January 31, 2013.
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(3) DRCR (Protocol N)

Evaluation of Results 1 Year Following Short-term Use of Ranibizumab for Vitreous Hemorrhage Due to Proliferative Diabetic Retinopathy

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JAMA Ophthalmol. 2014;132(7):889-890.

Vitreous hemorrhage from proliferative diabetic retinopathy can cause vision loss and preclude panretinal photocoagulation (PRP).[1] The Diabetic Retinopathy Clinical Research Network (DRCR.net) investigated whether intravitreal ranibizumab compared with intravitreal saline had a beneficial effect on the vitrectomy rates of eyes with vitreous hemorrhage from proliferative diabetic retinopathy precluding complete PRP. Eyes were randomly assigned to 0.5 mg of ranibizumab (n = 125) or saline (n = 136), which was injected into the vitreous at baseline, 4 weeks, and 8 weeks.[2] The primary end point was assessed at 16 weeks; for safety purposes, participants were followed for 52 weeks. After 16 weeks, each participant's management was at the investigators' discretion.

As previously reported, by the 16-week end point, the cumulative probability of vitrectomy was 12% for eyes assigned to ranibizumab compared with 17% for saline (difference, 4%; 95% CI, −4% to 13%),[2] suggesting little likelihood of a clinically important difference. The study did not address whether ranibizumab or saline injections were superior to observation alone. Previously reported secondary outcomes suggested a short-term positive biological effect of ranibizumab compared with saline: (1) the ability to complete PRP without vitrectomy by 16 weeks was 44% for the ranibizumab group vs 31% for the saline group ($P = .05$); (2) the mean (SD) visual acuity improvement from baseline to 12 weeks was 22 (23) letters with ranibizumab vs 16 (31) letters with saline ($P = .04$); and (3) recurrent vitreous hemorrhage within 16 weeks occurred in 6% of eyes with ranibizumab compared with 17% of eyes with saline ($P = .01$). No short-term safety concerns were noted. Herein, we present the 1-year follow-up results to the original study.

Results

Overall, 82% of the participants completed a 52-week visit, 2% died, and 16% were lost to follow-up. The 1-year cumulative probability of vitrectomy was 35% for the ranibizumab group vs 41% for the saline group (difference, 5%; 95% CI, −7% to 17%; $P = .35$) (Figure 1). The combined 1-year cumulative probability of vitrectomy in both groups was 38% (95% CI, 32% to 44%). The cumulative probability of complete PRP by the 52-week visit was 55% for the ranibizumab group vs 42% for the saline group ($P = .04$) (Figure 2). The mean (SD) visual acuity letter score at 52 weeks was 65 (22) (approximate Snellen equivalent, 20/50 ± 4.4 lines) in the ranibizumab group vs 64 (26) (approximate Snellen equivalent, 20/50 ± 5.2 lines) in the saline group ($P = .83$). Between 16 and 52 weeks of follow-up, 17 eyes in the ranibizumab group received 34 anti–vascular endothelial growth factor injections and 31 eyes in the saline group received 46 anti–vascular endothelial growth factor injections. Following the 16-week end point, investigator-reported recurrent vitreous hemorrhage appeared similar between treatment groups (13 of 102 eyes in the ranibizumab group and 15 of 113 eyes in the saline group). After 16 weeks, traction and/or rhegmatogenous retinal detachments on clinical examination or ultrasonography were seen in 7 eyes in the ranibizumab group compared with 11 eyes in the saline group. Three participants in the ranibizumab group (2%) and 8 participants in the saline group (6%) had an Antiplatelet Trialists' Collaboration–defined systemic adverse event ($P = .22$)

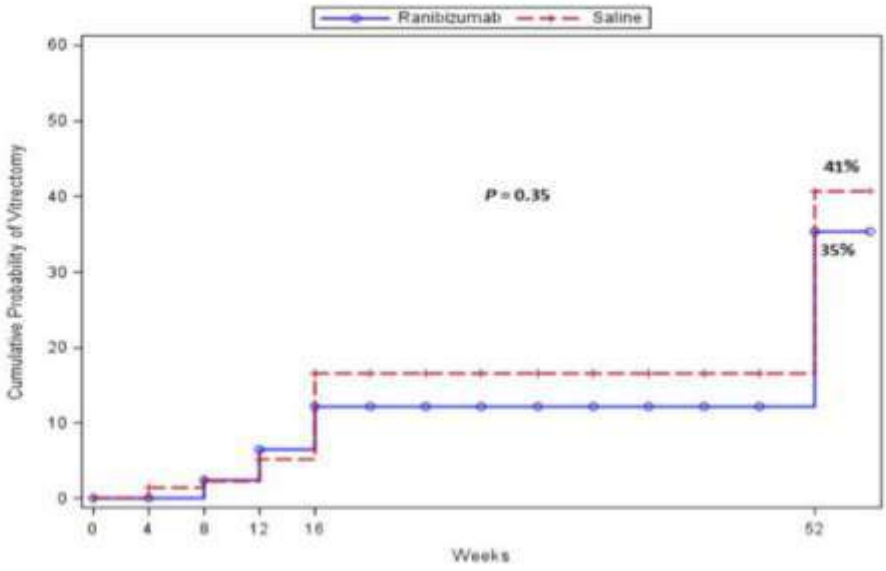

Figure 1.

Cumulative Probability of Vitrectomy Surgery by 52 Weeks of Study Follow-up

Categorization of events and censoring into intervals were defined by the visit date if the visit occurred; otherwise, they were defined using the target date of the visit. The number of eyes at risk indicates those with follow-up data at the start of the interval and no vitrectomy prior to the start of the interval; the number of events indicates the number of eyes with vitrectomy during the subsequent 4-week period. No follow-up was performed between 16 and 52 weeks. NA indicates not applicable.

Figure 2

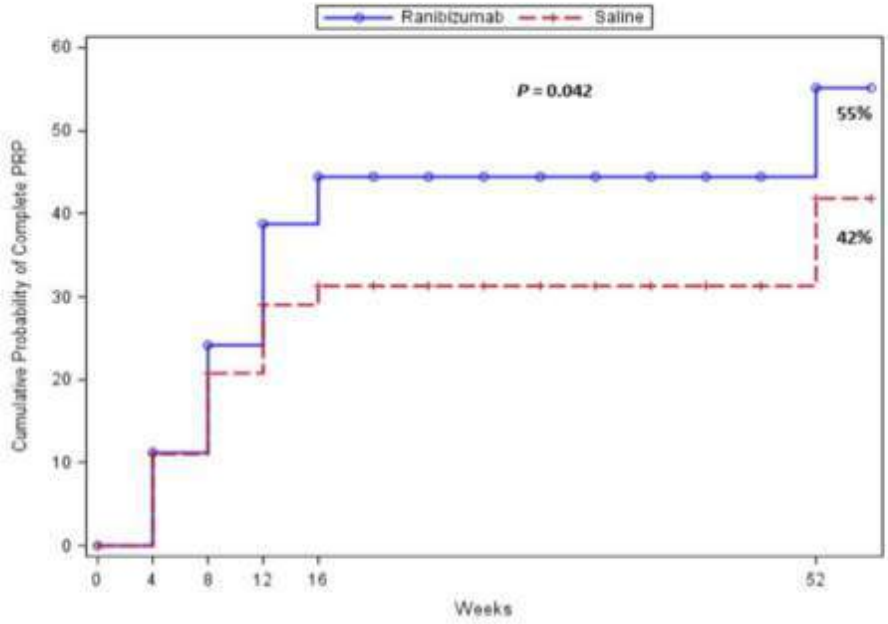

Figure 2.

Cumulative Probability of Complete Panretinal Photocoagulation by 16 Weeks of Study Follow-up

Categorization of events and censoring into intervals were defined by the visit date if the visit occurred; otherwise, they were defined using the target date of the visit. Eyes with vitrectomy were censored in the interval in which the surgery occurred. The number of eyes at risk indicates those with follow-up data at the start of the interval and with no complete panretinal photocoagulation prior to the start of the interval; the number of events indicates the number of eyes with complete panretinal photocoagulation during the subsequent 4-week period. No follow-up was performed between 16 and 52 weeks. NA indicates not applicable.

Discussion

More than one-third of eyes enrolled in the study underwent vitrectomy in both groups by 1 year. The ability to perform PRP occurred more frequently in the ranibizumab group; however, the greater improvement in mean visual acuity observed at 12 weeks was not present at 52 weeks. By the 52-week visit, there were no apparent differences on safety outcomes between the 2 interventions.

The evaluation of intravitreal saline vs ranibizumab given at baseline, 4 weeks, and 8 weeks after randomization in eyes with vitreous hemorrhage showed no difference in safety between the 2 treatment groups at 52 weeks. The absence of any clinically relevant differences in rates of vitrectomy noted through the primary end point at 16 weeks persisted through the 52-week safety follow-up.

(4) DRCR (Protocol S)

Panretinal Photocoagulation vs Intravitreous Ranibizuma for Proliferative Diabetic Retinopathy
A Randomized Clinical Trial

JAMA. 2015 Nov 13:1-11

IMPORTANCE Panretinal photocoagulation (PRP) is the standard treatment for reducing severe visual loss from proliferative diabetic retinopathy. However, PRP can damage the retina, resulting in peripheral vision loss or worsening diabetic macular edema (DME).

OBJECTIVE To evaluate the noninferiority of intravitreous ranibizumab compared with PRP for visual acuity outcomes in patients with proliferative diabetic retinopathy.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted at 55 US sites among 305 adults with proliferative diabetic retinopathy enrolled between February and December 2012 (mean age, 52 years; 44% female; 52% white). Both eyes were enrolled for 89 participants (1 eye to each study group), with a total of 394 study eyes. The final 2-year visit was completed in January 2015.

INTERVENTIONS Individual eyes were randomly assigned to receive PRP treatment, completed in 1 to 3 visits (n = 203 eyes), or ranibizumab, 0.5 mg, by intravitreous injection a baseline and as frequently as every 4 weeks based on a structured re-treatment protocol (n = 191 eyes). Eyes in both treatment groups could receive ranibizumab for DME.

MAIN OUTCOMES AND MEASURES The primary outcome was mean visual acuity change at 2 years (5-letter noninferiority margin; intention-to-treat analysis). Secondary outcomes included visual acuity area under the curve, peripheral visual field loss, vitrectomy, DME development, and retinal neovascularization.

RESULTS Mean visual acuity letter improvement at 2 years was +2.8 in the ranibizumab grou vs +0.2 in the PRP group (difference, +2.2; 95% CI, −0.5 to +5.0; $P < .001$ for noninferiority) The mean treatment group difference in visual acuity area under the curve over 2 years was +4.2 (95% CI, +3.0 to +5.4; $P < .001$). Mean peripheral visual field sensitivity loss was worse (−23 dB vs −42.2 dB; difference, 37.2 dB; 95% CI, 21.3-53.1 dB; $P < .001$), vitrectomy was more frequent (15% vs 4%; difference, 9%; 95% CI, 4%-15%; $P < .001$), and DME development w more frequent (28% vs 9%; difference, 19%; 95% CI, 10%-28%; $P < .001$) in the PRP group vs the ranibizumab group, respectively. Eyes without active or regressed neovascularization at 2 years were not significantly different (35% in the ranibizumab group vs 30% in the PRP group; difference, 3%; 95% CI, −7% to 12%; $P = .58$). One eye in the ranibizumab group developed endophthalmitis. No significant differences between groups in rates of major cardiovascular events were identified.

CONCLUSIONS AND RELEVANCE Among eyes with proliferative diabetic retinopathy, treatment with ranibizumab resulted in visual acuity that was noninferior to (not worse than PRP treatment at 2 years. Although longer-term follow-up is needed, ranibizumab may be a reasonable treatment alternative, at least through 2 years, for patients with proliferative diabetic retinopathy.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01489189

(5)DRCR (Protocol T-1 Year)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 26, 2015 VOL. 372 NO. 13

Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema

The Diabetic Retinopathy Clinical Research Network*

BACKGROUND

The relative efficacy and safety of intravitreous aflibercept, bevacizumab, and ranibizumab in the treatment of diabetic macular edema are unknown.

METHODS

At 89 clinical sites, we randomly assigned 660 adults (mean age, 61±10 years) with diabetic macular edema involving the macular center to receive intravitreous aflibercept at a dose of 2.0 mg (224 participants), bevacizumab at a dose of 1.25 mg (218 participants), or ranibizumab at a dose of 0.3 mg (218 participants). The study drugs were administered as often as every 4 weeks, according to a protocol-specified algorithm. The primary outcome was the mean change in visual acuity at 1 year.

RESULTS

From baseline to 1 year, the mean visual-acuity letter score (range, 0 to 100, with higher scores indicating better visual acuity; a score of 85 is approximately 20/20) improved by 13.3 with aflibercept, by 9.7 with bevacizumab, and by 11.2 with ranibizumab. Although the improvement was greater with aflibercept than with the other two drugs ($P<0.001$ for aflibercept vs. bevacizumab and $P=0.03$ for aflibercept vs. ranibizumab), it was not clinically meaningful, because the difference was driven by the eyes with worse visual acuity at baseline ($P<0.001$ for interaction). When the initial visual-acuity letter score was 78 to 69 (equivalent to approximately 20/32 to 20/40) (51% of participants), the mean improvement was 8.0 with aflibercept, 7.5 with bevacizumab, and 8.3 with ranibizumab ($P>0.50$ for each pairwise comparison). When the initial letter score was less than 69 (approximately 20/50 or worse), the mean improvement was 18.9 with aflibercept, 11.8 with bevacizumab, and 14.2 with ranibizumab ($P<0.001$ for aflibercept vs. bevacizumab, $P=0.003$ for aflibercept vs. ranibizumab, and $P=0.21$ for ranibizumab vs. bevacizumab). There were no significant differences among the study groups in the rates of serious adverse events ($P=0.40$), hospitalization ($P=0.51$), death ($P=0.72$), or major cardiovascular events ($P=0.56$).

CONCLUSIONS

Intravitreous aflibercept, bevacizumab, or ranibizumab improved vision in eyes with center-involved diabetic macular edema, but the relative effect depended on baseline visual acuity. When the initial visual-acuity loss was mild, there were no apparent differences, on average, among study groups. At worse levels of initial visual acuity, aflibercept was more effective at improving vision. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT01627249.)

(5)DRCR (Protocol T-2 Years)

Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema

Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial

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Purpose: To provide 2-year results comparing anti–vascular endothelial growth factor (VEGF) agents for center-involved diabetic macular edema (DME) using a standardized follow-up and retreatment regimen.

Design: Randomized clinical trial.

Participants: Six hundred sixty participants with visual acuity (VA) impairment from DME.

Methods: Randomization to 2.0-mg aflibercept, 1.25-mg repackaged (compounded) bevacizumab, or 0.3-mg ranibizumab intravitreous injections performed up to monthly using a protocol-specific follow-up and retreatment regimen. Focal/grid laser photocoagulation was added after 6 months if DME persisted. Visits occurred every 4 weeks during year 1 and were extended up to every 4 months thereafter when VA and macular thickness were stable.

Main Outcome Measures: Change in VA, adverse events, and retreatment frequency.

Results: Median numbers of injections were 5, 6, and 6 in year 2 and 15, 16, and 15 over 2 years in the aflibercept, bevacizumab, and ranibizumab groups, respectively (global $P = 0.08$). Focal/grid laser photocoagulation was administered in 41%, 64%, and 52%, respectively (aflibercept vs. bevacizumab, $P < 0.001$; aflibercept vs. ranibizumab, $P = 0.04$; bevacizumab vs. ranibizumab, $P = 0.01$). At 2 years, mean VA improved by 12.8, 10.0, and 12.3 letters, respectively. Treatment group differences varied by baseline VA ($P = 0.02$ for interaction). With worse baseline VA (20/50 to 20/320), mean improvement was 18.1, 13.3, and 16.1 letters, respectively (aflibercept vs. bevacizumab, $P = 0.02$; aflibercept vs. ranibizumab, $P = 0.18$; ranibizumab vs. bevacizumab, $P = 0.18$). With better baseline VA (20/32 to 20/40), mean improvement was 7.8, 6.8, and 8.6 letters, respectively ($P > 0.10$, for pairwise comparisons). Anti-Platelet Trialists' Collaboration (APTC) events occurred in 5% with aflibercept, 8% with bevacizumab, and 12% with ranibizumab (global $P = 0.047$; aflibercept vs. bevacizumab, $P = 0.34$; aflibercept vs. ranibizumab, $P = 0.047$; ranibizumab vs. bevacizumab, $P = 0.20$; global $P = 0.09$ adjusted for potential confounders).

Conclusions: All 3 anti-VEGF groups showed VA improvement from baseline to 2 years with a decreased number of injections in year 2. Visual acuity outcomes were similar for eyes with better baseline VA. Among eyes with worse baseline VA, aflibercept had superior 2-year VA outcomes compared with bevacizumab, but superiority of aflibercept over ranibizumab, noted at 1 year, was no longer identified. Higher APTC event rates with ranibizumab over 2 years warrants continued evaluation in future trials. *Ophthalmology 2016;■:1–9 © 2016 by the American Academy of Ophthalmology.*

RANIBIZUMAB PLUS PROMPT OR DEFERRED LASER FOR DIABETIC MACULAR EDEMA IN EYES WITH VITRECTOMY BEFORE ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY

Background: The approach to managing diabetic macular edema in eyes with previous vitrectomy is based on limited evidence. Therefore, an exploratory post hoc assessment of 3-year data from eyes with and without vitrectomy before randomization in a DRCR.net trial that evaluated ranibizumab + prompt or deferred laser for diabetic macular edema is presented.

Methods: Visual acuity and optical coherence tomography outcomes were compared between eyes with and without previous vitrectomy.

Results: At baseline, eyes with previous vitrectomy (n = 25) had longer duration of diabetes, worse visual acuity, less thickened central subfield measurements on optical coherence tomography and were more apt to have worse diabetic retinopathy severity level or previous treatment for macular edema or cataract surgery than eyes without a history of vitrectomy (n = 335). Analyses adjusted for these baseline imbalances did not identify substantial differences between eyes with and without previous vitrectomy at each annual visit through 3 years for the favorable visual acuity, optical coherence tomography central subfield thickness, or volume outcomes, although optical coherence tomography improvement appeared slower in vitrectomy eyes during the first year.

Conclusion: This study provides little evidence that the beneficial clinical outcomes for patients with center-involved diabetic macular edema treated with anti-vascular endothelial growth factor are affected in the long term by previous vitrectomy.

RETINA 35:2516–2528, 2015

(6) DRCR (Protocol U)

JAMA Ophthalmology | Original Investigation

Effect of Adding Dexamethasone to Continued Ranibizumab Treatment in Patients With Persistent Diabetic Macular Edema

A DRCR Network Phase 2 Randomized Clinical Trial

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IMPORTANCE Some eyes have persistent diabetic macular edema (DME) following anti-vascular endothelial growth factor (anti-VEGF) therapy for DME. Subsequently adding intravitreous corticosteroids to the treatment regimen might result in better outcomes than continued anti-VEGF therapy alone.

OBJECTIVE To compare continued intravitreous ranibizumab alone with ranibizumab plus intravitreous dexamethasone implant in eyes with persistent DME.

DESIGN, SETTING, AND PARTICIPANTS Phase 2 multicenter randomized clinical trial conducted at 40 US sites in 129 eyes from 116 adults with diabetes between February 2014 and December 2016. Eyes had persistent DME, with visual acuity of 20/32 to 20/320 after at least 3 anti-VEGF injections before a run-in phase, which included an additional 3 monthly 0.3-mg ranibizumab injections. Data analysis was according to intent to treat.

INTERVENTIONS Following the run-in phase, study eyes that had persistent DME and were otherwise eligible were randomly assigned to receive 700 µg of dexamethasone (combination group, 65 eyes) or sham treatment (ranibizumab group, 64 eyes) in addition to continued 0.3-mg ranibizumab in both treatment arms as often as every 4 weeks based on a structured re-treatment protocol.

MAIN OUTCOMES AND MEASURES The primary outcome was change in mean visual acuity letter score at 24 weeks as measured by the electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS). The principal secondary outcome was change in mean central subfield thickness as measured with the use of optical coherence tomography.

RESULTS Of the 116 randomized patients, median age was 65 years (interquartile range [IQR], 58-71 years); 50.9% were female and 60.3% were white. Mean (SD) improvement in visual acuity from randomization was 2.7 (9.8) letters in the combination group and 3.0 (7.1) letters in the ranibizumab group, with the adjusted treatment group difference (combination minus ranibizumab) of -0.5 letters (95% CI, -3.6 to 2.5; 2-sided $P = .73$). Mean (SD) change in central subfield thickness in the combination group was -110 (86) µm compared with -62 (97) µm for the ranibizumab group (adjusted difference, -52; 95% CI, -82 to -22; 2-sided $P < .001$). Nineteen eyes (29%) in the combination group experienced increased intraocular pressure or initiated treatment with antihypertensive eyedrops compared with 0 in the ranibizumab group (2-sided $P < .001$).

CONCLUSIONS AND RELEVANCE Although its use is more likely to reduce retinal thickness and increase intraocular pressure, the addition of intravitreous dexamethasone to continued ranibizumab therapy does not improve visual acuity at 24 weeks more than continued ranibizumab therapy alone among eyes with persistent DME following anti-VEGF therapy.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01945866

JAMA Ophthalmol. doi:10.1001/jamaophthalmol.2017.4914
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(7) READ-1 Study

Vascular Endothelial Growth Factor Is a Critical Stimulus for Diabetic Macular Edema

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Am J Ophthalmol. 2006 Dec;142(6):961-9.

Abstract

PURPOSE: The role of vascular endothelial growth factor (VEGF) in diabetic macular edema (DME) was tested with ranibizumab, a specific antagonist of VEGF.

DESIGN: A nonrandomized clinical trial.

METHODS: Ten patients with chronic DME received intraocular injections of 0.5 mg of ranibizumab at baseline and at one, two, four, and six months. The primary outcome was change in foveal thickness between baseline and seven months, and the secondary outcome measures were changes from baseline in visual acuity and macular volume.

RESULTS: Mean values at baseline were 503 micron for foveal thickness, 9.22 mm3 for macular volume, and 28.1 letters (20/80) read on an Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart. At seven months (one month after the fifth injection), the mean foveal thickness was 257 micron, which was a reduction of 246 micron (85% of the excess foveal thickness present at baseline; P = .005 by Wilcoxon signed-rank test for likelihood that this change is due to ranibizumab rather than chance). The macular volume was 7.47 mm3, which was a reduction of 1.75 mm3 (77% of the excess macular volume at baseline; P = .009). Mean visual acuity was 40.4 letters (20/40), which was an improvement of 12.3 letters (P = .005). The injections were well-tolerated with no ocular or systemic adverse events.

CONCLUSION: Intraocular injections of ranibizumab significantly reduced foveal thickness and improved visual acuity in 10 patients with DME, which demonstrated that VEGF is an important therapeutic target for DME. A randomized, controlled, double-masked trial is needed to test whether intraocular injections of ranibizumab provide long-term benefit to patients with DME.