Clinical Trials in Diabetic Retinopathy

2018

Harry W. Flynn Jr., M.D.
Nidhi Relhan Batra, M.D.

Bascom Palmer Eye Institute
900 N.W. 17th Street
Miami, FL 33136
Phone: (305) 326-6118
Fax: (305) 326-6417
E-mail: hflynn@med.miami.edu

Clinical Trials in Diabetic Retinopathy

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.

Lancet 2017; 389: 2193–203

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

(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)

Intravitreal Ranibizumab for Diabetic Macular Edema with Prompt versus Deferred Laser Treatment: 5-Year Randomized Trial Results

Michael J. Elman, MD,[1] Allison Ayala, MS,[2] Neil M. Bressler, MD,[3] David Browning, MD,[4] Christina J. Flaxel, MD,[5] Adam R. Glassman, MS,[2] Lee M. Jampol, MD,[6] Thomas W. Stone, MD,[7] for the Diabetic Retinopathy Clinical Research Network

Objective: To report 5-year results from a previously reported trial evaluating intravitreal 0.5 mg ranibizumab with prompt versus deferred (for ≥24 weeks) focal/grid laser treatment for diabetic macular edema (DME).

Design: Multicenter, randomized clinical trial.

Participants: Among participants from the trial with 3 years of follow-up who subsequently consented to a 2-year extension and survived through 5 years, 124 (97%) and 111 (92%) completed the 5-year visit in the prompt and deferred groups, respectively.

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

Main Outcome Measures: Best-corrected visual acuity at the 5-year visit.

Results: The mean change in visual acuity letter score from baseline to the 5-year visit was +7.2 letters in the prompt laser group compared with +9.8 letters in the deferred laser group (mean difference, −2.6 letters; 95% confidence interval, −5.5 to +0.4 letters; $P = 0.09$). At the 5-year visit in the prompt versus deferred laser groups, there was vision loss of ≥10 letters in 9% versus 8%, an improvement of ≥10 letters in 46% versus 58%, and an improvement of ≥15 letters in 27% versus 38% of participants, respectively. From baseline to 5 years, 56% of participants in the deferred group did not receive laser. The median number of injections was 13 versus 17 in the prompt and deferral groups, including 54% and 45% receiving no injections during year 4 and 62% and 52% receiving no injections during year 5, respectively.

Conclusions: Five-year results suggest focal/grid laser treatment at the initiation of intravitreal ranibizumab is no better than deferring laser treatment for ≥24 weeks in eyes with DME involving the central macula with vision impairment. Although more than half of eyes in which laser treatment is deferred may avoid laser for at least 5 years, such eyes may require more injections to achieve these results when following this protocol. Most eyes treated with ranibizumab and either prompt or deferred laser maintain vision gains obtained by the first year through 5 years with little additional treatment after 3 years. *Ophthalmology 2015;122:375-381 © 2015 by the American Academy of Ophthalmology.*

(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

Susan B. Bressler, MD[1], Michele Melia, ScM[2], Adam R. Glassman, MS[2], Talat Almukhtar, MBChB[2], Lee M. Jampol, MD[3], Michel Shami, MD[4], Brian B. Berger, MD[5], Neil M Bressler, MD[1], and the Diabetic Retinopathy Clinical Research Network.

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.
doi:10.1001/jamaophthalmol.2013.2015

(3) DRCR (Protocol N)

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

Abdhish R. Bhavsar, MD[1]; Karisse Torres, MPH[2]; Adam R. Glassman, MS[2]; Lee M. Jampol, MD[3]; James L. Kinyoun, MD[4] ; for the Diabetic Retinopathy Clinical Research Network

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 ($P = .22$).

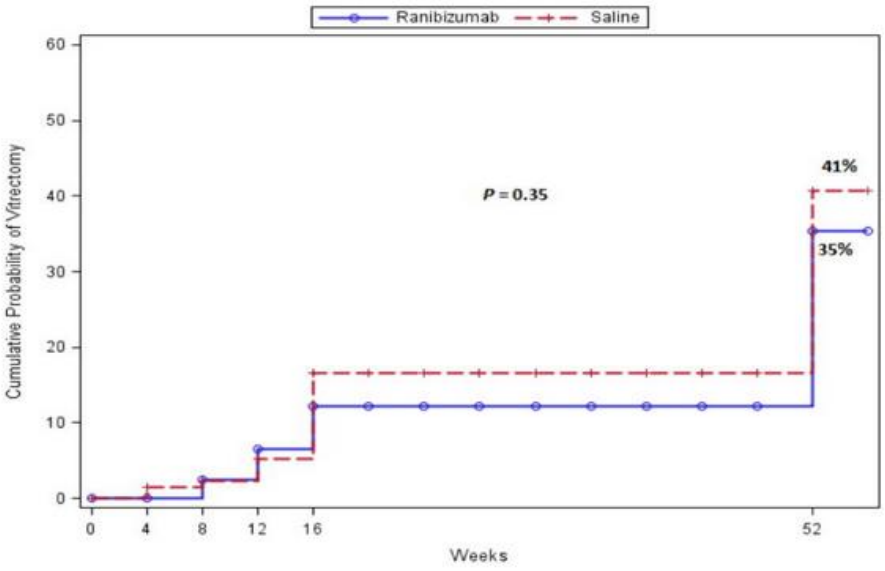

Figure 1.

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

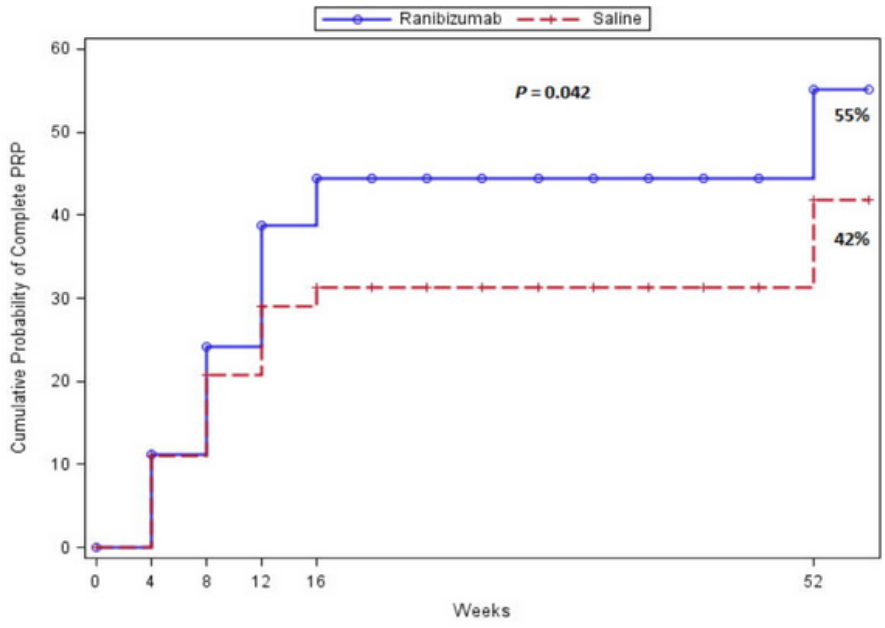

Figure 2.

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 – 2 years)

Panretinal Photocoagulation vs Intravitreous Ranibizumab 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 at 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 group 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 −422 dB; difference, 372 dB; 95% CI, 213-531 dB; $P < .001$), vitrectomy was more frequent (15% vs 4%; difference, 9%; 95% CI, 4%-15%; $P < .001$), and DME development was 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

(4) DRCR (Protocol S – 5 years)

JAMA Ophthalmology | Original Investigation

Five-Year Outcomes of Panretinal Photocoagulation vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy
A Randomized Clinical Trial

Jeffrey G. Gross, MD; Adam R. Glassman, MS; Danni Liu, MSPH; Jennifer K. Sun, MD, MPH; Andrew N. Antoszyk, MD; Carl W. Baker, MD; Neil M. Bressler, MD; Michael J. Elman, MD; Frederick L. Ferris III, MD; Thomas W. Gardner, MD, MS; Lee M. Jampol, MD; Daniel F. Martin, MD; Michele Melia, ScM; Cynthia R. Stockdale, MSPH; Roy W. Beck, MD, PhD; for the Diabetic Retinopathy Clinical Research Network

IMPORTANCE Ranibizumab is a viable treatment option for eyes with proliferative diabetic retinopathy (PDR) through 2 years. However, longer-term results are needed.

OBJECTIVE To evaluate efficacy and safety of 0.5-mg intravitreous ranibizumab vs panretinal photocoagulation (PRP) over 5 years for PDR.

DESIGN, SETTING, AND PARTICIPANTS Diabetic Retinopathy Clinical Research Network multicenter randomized clinical trial evaluated 394 study eyes with PDR enrolled February through December 2012. Analysis began in January 2018.

INTERVENTIONS Eyes were randomly assigned to receive intravitreous ranibizumab (n = 191) or PRP (n = 203). Frequency of ranibizumab was based on a protocol-specified retreatment algorithm. Diabetic macular edema could be managed with ranibizumab in either group.

MAIN OUTCOMES AND MEASURES Mean change in visual acuity (intention-to-treat analysis) was the main outcome. Secondary outcomes included peripheral visual field loss, development of vision-impairing diabetic macular edema, and ocular and systemic safety.

RESULTS The 5-year visit was completed by 184 of 277 participants (66% excluding deaths). Of 305 enrolled participants, the mean (SD) age was 52 (12) years, 135 (44%) were women, and 160 (52%) were white. For the ranibizumab and PRP groups, the mean (SD) number of injections over 5 years was 19.2 (10.9) and 5.4 (7.9), respectively; the mean (SD) change in visual acuity letter score was 3.1 (14.3) and 3.0 (10.5) letters, respectively (adjusted difference, 0.6; 95% CI, −2.3 to 3.5; *P* = .68); the mean visual acuity was 20/25 (approximate Snellen equivalent) in both groups at 5 years. The mean (SD) change in cumulative visual field total point score was −330 (645) vs −527 (635) dB in the ranibizumab (n = 41) and PRP (n = 38) groups, respectively (adjusted difference, 208 dB; 95% CI, 9-408). Vision-impairing diabetic macular edema developed in 27 and 53 eyes in the ranibizumab and PRP groups, respectively (cumulative probabilities: 22% vs 38%; hazard ratio, 0.4; 95% CI, 0.3-0.7). No statistically significant differences between groups in major systemic adverse event rates were identified.

CONCLUSIONS AND RELEVANCE Although loss to follow-up was relatively high, visual acuity in most study eyes that completed follow-up was very good at 5 years and was similar in both groups. Severe vision loss or serious PDR complications were uncommon with PRP or ranibizumab; however, the ranibizumab group had lower rates of developing vision-impairing diabetic macular edema and less visual field loss. Patient-specific factors, including anticipated visit compliance, cost, and frequency of visits, should be considered when choosing treatment for patients with PDR. These findings support either anti–vascular endothelial growth factor therapy or PRP as viable treatments for patients with PDR.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01489189

JAMA Ophthalmol. doi:10.1001/jamaophthalmol.2018.3255
Published online July 24, 2018.

(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

John A. Wells, MD,[1] Adam R. Glassman, MS,[2] Allison R. Ayala, MS,[2] Lee M. Jampol, MD,[3] Neil M. Bressler, MD,[4] Susan B. Bressler, MD,[4] Alexander J. Brucker, MD,[5] Frederick L. Ferris, MD,[6] G. Robert Hampton, MD,[7] Chirag Jhaveri, MD,[8] Michele Melia, ScM,[2] Roy W. Beck, MD, PhD,[2] for the Diabetic Retinopathy Clinical Research Network

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

Raj K. Maturi, MD; Adam R. Glassman, MS; Danni Liu, MSPH; Roy W. Beck, MD; Abdhish R. Bhavsar, MD; Neil M. Bressler, MD; Lee M. Jampol, MD; Michele Melia, ScM; Omar S. Punjabi, MD; Hani Salehi-Had, MD; Jennifer K. Sun, MD; for the Diabetic Retinopathy Clinical Research Network

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
Published online November 11, 2017.

(7) READ-1 Study

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

QUAN DONG NGUYEN, MD, MSc, SINAN TATLIPINAR, MD, SYED MAHMOOD SHAH, MBBS, JULIA A. HALLER, MD, EDWARD QUINLAN, MD, JENNIFER SUNG, MD, INGRID ZIMMER-GALLER, MD, DIANA V. DO, MD, AND PETER A. CAMPOCHIARO, MD

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.

(8) READ-2 Study

Primary End Point (Six Months) Results of the Ranibizumab for Edema of the mAcula in Diabetes (READ-2) Study

*Quan Dong Nguyen, MD, MSc,[1] Syed Mahmood Shah, MBBS,[1,2] Jeffery S. Heier, MD,[3] Diana V. Do, MD,[1] Jennifer Lim, MD,[4] David Boyer, MD,[5] Prema Abraham, MD,[6] Peter A. Campochiaro, MD,[1] for the READ-2 Study Group**

Objectives: To compare ranibizumab with focal/grid laser or a combination of both in diabetic macular edema (DME).

Design: Prospective, randomized, interventional, multicenter clinical trial.

Participants: A total of 126 patients with DME.

Methods: Subjects were randomized 1:1:1 to receive 0.5 mg of ranibizumab at baseline and months 1, 3, and 5 (group 1, 42 patients), focal/grid laser photocoagulation at baseline and month 3 if needed (group 2, 42 patients), or a combination of 0.5 mg of ranibizumab and focal/grid laser at baseline and month 3 (group 3, 42 patients).

Main Outcome Measures: The primary end point was the change from baseline in best-corrected visual acuity (BCVA) at month 6.

Results: At month 6, the mean gain in BCVA was significantly greater in group 1 (+7.24 letters, $P = 0.01$, analysis of variance) compared with group 2 (−0.43 letters), and group 3 (+3.80 letters) was not statistically different from groups 1 or 2. For patients with data available at 6 months, improvement of 3 lines or more occurred in 8 of 37 (22%) in group 1 compared with 0 of 38 (0%) in group 2 ($P = 0.002$, Fisher exact test) and 3 of 40 (8%) in group 3. Excess foveal thickness was reduced by 50%, 33%, and 45% in groups 1, 2, and 3, respectively.

Conclusions: During a span of 6 months, ranibizumab injections by the current protocol had a significantly better visual outcome than focal/grid laser treatment in patients with DME.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2009;116:2175–2181

(8) READ-2 Study (Two-Year Outcomes)

Two-Year Outcomes of the Ranibizumab for Edema of the mAcula in Diabetes (READ-2) Study

*Quan Dong Nguyen, MD, MSc,[1] Syed Mahmood Shah, MBBS,[1,2] Afsheen A. Khwaja, MD,[1] Roomasa Channa, MD,[1] Elham Hatef, MD,[1] Diana V. Do, MD,[1] David Boyer, MD,[3] Jeffery S. Heier, MD,[4] Prema Abraham, MD,[5] Allen B. Thach, MD,[6] Eugene S. Lit, MD,[7] Bradley S. Foster, MD,[8] Erik Kruger, MD,[9] Pravin Dugel, MD,[10] Thomas Chang, MD,[11] Arup Das, MD,[12] Thomas A. Ciulla, MD,[13] John S. Pollack, MD,[14] Jennifer I. Lim, MD,[15] Dean Eliot, MD,[16] Peter A. Campochiaro, MD,[1] for the READ-2 Study Group**

Objectives: To determine the long-term effects of ranibizumab (RBZ) in patients with diabetic macular edema (DME).

Design: Prospective, randomized, interventional, multicenter clinical trial.

Participants: One hundred twenty-six patients with DME.

Methods: Subjects were randomized 1:1:1 to receive 0.5 mg RBZ at baseline and months 1, 3, and 5 (group 1), focal or grid laser photocoagulation at baseline and month 3 if needed (group 2), or a combination of 0.5 mg RBZ and focal or grid laser at baseline and month 3 (group 3). Starting at month 6, if retreatment criteria were met, all subjects could be treated with RBZ.

Main Outcome Measures: The mean change from baseline in best-corrected visual acuity (BCVA) at month 24.

Results: After the primary end point at month 6, most patients in all groups were treated only with RBZ, and the mean number of injections was 5.3, 4.4, and 2.9 during the 18-month follow-up period in groups 1, 2, and 3, respectively. For the 33 patients in group 1, 34 patients in group 2, and 34 patients in group 3 who remained in the study through 24 months, the mean improvement in BCVA was 7.4, 0.5, and 3.8 letters at the 6-month primary end point, compared with 7.7, 5.1, and 6.8 letters at month 24, and the percentage of patients who gained 3 lines or more of BCVA was 21, 0, and 6 at month 6, compared with 24, 18, and 26 at month 24. The percentage of patients with 20/40 or better Snellen equivalent at month 24 was 45% in group 1, 44% in group 2, and 35% in group 3. Mean foveal thickness (FTH), defined as center subfield thickness, at month 24 was 340 μm, 286 μm, and 258 μm for groups 1, 2, and 3, respectively, and the percentage of patients with center subfield thickness of 250 μm or less was 36%, 47%, and 68%, respectively.

Conclusions: Intraocular injections of RBZ provided benefit for patients with DME for at least 2 years, and when combined with focal or grid laser treatments, the amount of residual edema was reduced, as were the frequency of injections needed to control edema.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2010;117:2146–2151

(9) RISE and RIDE Study

Long-term Outcomes of Ranibizumab Therapy for Diabetic Macular Edema: The 36-Month Results from Two Phase III Trials

RISE and RIDE

*David M. Brown, MD,[1,§] Quan Dong Nguyen, MD, MSc,[2,§] Dennis M. Marcus, MD,[3] David S. Boyer, MD,[4] Sunil Patel, MD, PhD,[5] Leonard Feiner, MD, PhD,[6] Patricio G. Schlottmann, MD,[7] Amy Chen Rundle, MS,[8] Jiameng Zhang, PhD,[8] Roman G. Rubio, MD,[8] Anthony P. Adamis, MD,[8] Jason S. Ehrlich, MD, PhD,[8] J. Jill Hopkins, MD,[8] on behalf of the RIDE and RISE Research Group**

Purpose: To report 36-month outcomes of RIDE (NCT00473382) and RISE (NCT00473330), trials of ranibizumab in diabetic macular edema (DME).

Design: Phase III, randomized, multicenter, double-masked, 3-year trials, sham injection–controlled for 2 years.

Participants: Adults with DME (n=759), baseline best-corrected visual acuity (BCVA) 20/40 to 20/320 Snellen equivalent, and central foveal thickness (CFT) ≥275 μm on optical coherence tomography.

Methods: Patients were randomized equally (1 eye per patient) to monthly 0.5 mg or 0.3 mg ranibizumab or sham injection. In the third year, sham patients, while still masked, were eligible to cross over to monthly 0.5 mg ranibizumab. Macular laser was available to all patients starting at month 3; panretinal laser was available as necessary.

Main Outcome Measures: The proportion of patients gaining ≥15 Early Treatment Diabetic Retinopathy Study letters in BCVA from baseline at month 24.

Results: Visual acuity (VA) outcomes seen at month 24 in ranibizumab groups were consistent through month 36; the proportions of patients who gained ≥15 letters from baseline at month 36 in the sham/0.5 mg, 0.3 mg, and 0.5 mg ranibizumab groups were 19.2%, 36.8%, and 40.2%, respectively, in RIDE and 22.0%, 51.2%, and 41.6%, respectively, in RISE. In the ranibizumab arms, reductions in CFT seen at 24 months were, on average, sustained through month 36. After crossover to 1 year of treatment with ranibizumab, average VA gains in the sham/0.5 mg group were lower compared with gains seen in the ranibizumab patients after 1 year of treatment (2.8 vs. 10.6 and 11.1 letters). Per-injection rates of endophthalmitis remained low over time (~0.06% per injection). The incidence of serious adverse events potentially related to systemic vascular endothelial growth factor inhibition was 19.7% in patients who received 0.5 mg ranibizumab compared with 16.8% in the 0.3 mg group.

Conclusions: The strong VA gains and improvement in retinal anatomy achieved with ranibizumab at month 24 were sustained through month 36. Delayed treatment in patients receiving sham treatment did not seem to result in the same extent of VA improvement observed in patients originally randomized to ranibizumab. Ocular and systemic safety was generally consistent with the results seen at month 24.

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

Ophthalmology 2013;120:2013-2022

(9) RIDE and RISE Study – Open-label Extension - Long Term Outcomes

Outcomes with As-Needed Ranibizumab after Initial Monthly Therapy

Long-Term Outcomes of the Phase III RIDE and RISE Trials

*David S. Boyer, MD,[1] Quan Dong Nguyen, MD, MSc,[2] David M. Brown, MD,[3] Karen Basu, PhD,[4] Jason S. Ehrlich, MD, PhD,[4] for the RIDE and RISE Research Group**

Purpose: To determine whether the efficacy and safety achieved with monthly ranibizumab as treatment for diabetic macular edema (DME) can be maintained with less-than-monthly treatment.

Design: Open-label extension (OLE) phase of randomized, sham-controlled phase III trials: RIDE (NCT00473382) and RISE (NCT00473330).

Participants: Five hundred of 582 adults who completed the 36-month randomized core studies elected to enter the OLE.

Methods: All patients participating in the OLE were eligible to receive 0.5 mg ranibizumab according to predefined re-treatment criteria: Treatment was administered when DME was identified by the investigator on optical coherence tomography or when best-corrected visual acuity (BCVA) worsened by ≥5 Early Treatment Diabetic Retinopathy Study letters versus month 36. Patients were observed at 30-, 60-, or 90-day intervals depending on the need for treatment.

Main Outcome Measures: The incidence and severity of ocular and nonocular events, proportion of patients with ≥15-letter best-corrected visual acuity (BCVA) gain from baseline, mean BCVA change from month 36 (final core study visit), mean central foveal thickness (CFT), and mean CFT change from month 36.

Results: A mean of 4.5 injections were administered over a mean follow-up of 14.1 months. Approximately 25% of patients did not require further treatment based on protocol-defined re-treatment criteria. Mean BCVA was sustained or improved in these patients through the end of follow-up. Approximately 75% of patients received ≥1 criteria-based re-treatment; mean time to first re-treatment was approximately 3 months after the last masked-phase visit. Mean BCVA remained stable in re-treated patients; CFT was generally stable with a trend toward slight thickening in all patients when mandatory monthly therapy was relaxed.

Conclusions: Vision gains achieved after 1 or 3 years of monthly ranibizumab therapy were maintained with a marked reduction in treatment frequency; some patients required no additional treatment. These observations are consistent with other studies evaluating induction followed by maintenance ranibizumab therapy for DME. Patients whose treatment was deferred by 2 years (randomized initially to sham) did not ultimately achieve the same BCVA gains as patients who received ranibizumab from baseline. Ranibizumab's safety profile in the OLE appeared similar to that observed in the controlled core studies and other studies. *Ophthalmology 2015;122:2504-2513*

(9) Results from RIDE and RISE

Vision-Related Function after Ranibizumab Treatment for Diabetic Macular Edema

*Neil M. Bressler, MD,[1] Rohit Varma, MD,[2] Ivan J. Suñer, MD,[3] Chantal M. Dolan, PhD,[4] James Ward, PhD,[4] Jason S. Ehrlich, MD, PhD,[4] Shoshana Colman, PhD,[4] Adam Turpcu, PhD,[4] for the RIDE and RISE Research Groups**

Objective: To examine the effects of intravitreal ranibizumab (Lucentis; Genentech, Inc., South San Fran- cisco, CA) treatment on patient-reported vision-related function, as assessed by 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) scores, in patients with visual impairment secondary to center- involved diabetic macular edema (DME).

Design: Within 2 randomized, double-masked, phase 3 clinical trials (RIDE [A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema {ME} With Center Involvement Secondary to Diabetes Mellitus; NCT00473382] and RISE [A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema {ME} With Center Involvement Secondary to Diabetes Mellitus; NCT00473330]), the NEI VFQ-25 was administered at baseline and at the 6-, 12-, 18-, and 24-month follow-up visits.

Participants: Three hundred eighty-two (100%) RIDE patients and 377 (100%) RISE patients.

Intervention: Patients were randomized 1:1:1 to monthly injections of intravitreal ranibizumab 0.3 or 0.5 mg or sham. Study participants could receive macular laser for DME from month 3 onward if specific criteria were met.

Main Outcome Measures: Exploratory post hoc analysis of mean change from baseline in NEI VFQ-25 scores at 12 and 24 months.

Results: Across all treatment arms, 13% to 28% of enrolled eyes were the better-seeing eye. For all eyes in RIDE and RISE, the mean change in NEI VFQ-25 composite score improved more in ranibizumab-treated eyes at both the 12- and 24-month visits compared with sham treatment. For the better-seeing eyes at baseline, the mean change in composite score with 0.3 mg ranibizumab at the 24-month visit was 10.9 more (95% confidence interval [CI], 2.5e19.2) than sham for RIDE patients and 1.3 more (95% CI, -10.5 to 13.0) than sham for RISE patients. For the worse-seeing eyes at baseline, the mean change in composite score with 0.3 mg rani- bizumab at the 24-month visit was 1.0 more (95% CI, -4.7 to 6.7) than sham for RIDE patients and 1.8 more (95% CI, -2.7 to 6.2) than sham for RISE patients. Similar results for most of these outcomes were seen with 0.5 mg ranibizumab.

Conclusions: These phase 3 trials demonstrated that ranibizumab treatment for DME likely improves patient-reported vision-related function outcomes compared with sham, further supporting treatment of DME with ranibizumab.

Ophthalmology 2014;-:1-12.

(10) RESTORE Study

The RESTORE Study

Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema

*Paul Mitchell, MD, PhD,[1] Francesco Bandello, MD, FEBO,[2] Ursula Schmidt-Erfurth, MD,[3] Gabriele E. Lang, MD,[4] Pascale Massin, MD, PhD,[5] Reinier O. Schlingemann, MD, PhD,[6] Florian Sutter, MD,[7] Christian Simader, MD,[8] Gabriela Burian, MD, MPH,[9] Ortrud Gerstner, MSc,[9] Andreas Weichselberger, PhD,[9] on behalf of the RESTORE study group**

Objective: To demonstrate superiority of ranibizumab 0.5 mg monotherapy or combined with laser over laser alone based on mean average change in best-corrected visual acuity (BCVA) over 12 months in diabetic macular edema (DME).

Design: A 12-month, randomized, double-masked, multicenter, laser-controlled phase III study.

Participants: We included 345 patients aged ≥18 years, with type 1 or 2 diabetes mellitus and visual impairment due to DME.

Methods: Patients were randomized to ranibizumab + sham laser (n = 116), ranibizumab + laser (n = 118), or sham injections + laser (n = 111). Ranibizumab/sham was given for 3 months then pro re nata (PRN); laser/sham laser was given at baseline then PRN (patients had scheduled monthly visits).

Main Outcome Measures: Mean average change in BCVA from baseline to month 1 through 12 and safety.

Results: Ranibizumab alone and combined with laser were superior to laser monotherapy in improving mean average change in BCVA letter score from baseline to month 1 through 12 (+6.1 and +5.9 vs +0.8; both $P<0.0001$). At month 12, a significantly greater proportion of patients had a BCVA letter score ≥15 and BCVA letter score level >73 (20/40 Snellen equivalent) with ranibizumab (22.6% and 53%, respectively) and ranibizumab + laser (22.9% and 44.9%) versus laser (8.2% and 23.6%). The mean central retinal thickness was significantly reduced from baseline with ranibizumab (−118.7 μm) and ranibizumab + laser (−128.3 μm) versus laser (−61.3 μm; both $P<0.001$). Health-related quality of life, assessed through National Eye Institute Visual Function Questionnaire (NEI VFQ-25), improved significantly from baseline with ranibizumab alone and combined with laser ($P<0.05$ for composite score and vision-related subscales) versus laser. Patients received ~7 (mean) ranibizumab/sham injections over 12 months. No endophthalmitis cases occurred. Increased intraocular pressure was reported for 1 patient each in the ranibizumab arms. Ranibizumab monotherapy or combined with laser was not associated with an increased risk of cardiovascular or cerebrovascular events in this study.

Conclusions: Ranibizumab monotherapy and combined with laser provided superior visual acuity gain over standard laser in patients with visual impairment due to DME. Visual acuity gains were associated with significant gains in VFQ-25 scores. At 1 year, no differences were detected between the ranibizumab and ranibizumab + laser arms. Ranibizumab monotherapy and combined with laser had a safety profile in DME similar to that in age-related macular degeneration.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2011;118:615–625

(11) BOLT Study

A Prospective Randomized Trial of Intravitreal Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema (BOLT Study)

12-Month Data: Report 2

Michel Michaelides, MD, FRCOphth,[1,2,] Andrew Kaines, FRANZCO,[1,*] Robin D. Hamilton, DM, FRCOphth,[1] Samantha Fraser-Bell, PhD, FRANZCO,[1] Ranjan Rajendram, MD, MRCOphth,[1,2] Fahd Quhill, FRCOphth,[1] Christopher J. Boos, MRCP, MD,[3] Wen Xing, BSc,[4] Catherine Egan, FRANZCO,[1] Tunde Peto, MD, PhD,[1,5] Catey Bunce, DSc,[4] R. David Leslie, MD, FRCP,[6] Philip G. Hykin, MD, FRCOphth[1]*

Purpose: To report the findings at 1 year of a study comparing repeated intravitreal bevacizumab (ivB) and modified Early Treatment of Diabetic Retinopathy Study (ETDRS) macular laser therapy (MLT) in patients with persistent clinically significant diabetic macular edema (CSME).

Design: Prospective, randomized, masked, single-center, 2-year, 2-arm clinical trial.

Participants: A total of 80 eyes of 80 patients with center-involving CSME and at least 1 prior MLT.

Methods: Subjects were randomized to either ivB (6 weekly; minimum of 3 injections and maximum of 9 injections in the first 12 months) or MLT (4 monthly; minimum of 1 treatment and maximum of 4 treatments in the first 12 months).

Main Outcome Measures: The primary end point was the difference in ETDRS best-corrected visual acuity (BCVA) at 12 months between the bevacizumab and laser arms.

Results: The baseline mean ETDRS BCVA was 55.7±9.7 (range 34–69) in the bevacizumab group and 54.6±8.6 (range 36–68) in the laser arm. The mean ETDRS BCVA at 12 months was 61.3±10.4 (range 34–79) in the bevacizumab group and 50.0±16.6 (range 8–76) in the laser arm ($P = 0.0006$). Furthermore, the bevacizumab group gained a median of 8 ETDRS letters, whereas the laser group lost a median of 0.5 ETDRS letters ($P = 0.0002$). The odds of gaining ≥10 ETDRS letters over 12 months were 5.1 times greater in the bevacizumab group than in the laser group (adjusted odds ratio, 5.1; 95% confidence interval, 1.3–19.7; $P = 0.019$). At 12 months, central macular thickness decreased from 507±145 μm (range 281–900 μm) at baseline to 378±134 μm (range 167–699 μm) ($P<0.001$) in the ivB group, whereas it decreased to a lesser extent in the laser group, from 481±121 μm (range 279–844 μm) to 413±135 μm (range 170–708 μm) ($P = 0.02$). The median number of injections was 9 (interquartile range [IQR] 8–9) in the ivB group, and the median number of laser treatments was 3 (IQR 2–4) in the MLT group.

Conclusions: The study provides evidence to support the use of bevacizumab in patients with center-involving CSME without advanced macular ischemia.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology 2010;117:1078–1086 © 2010 by the American Academy of Ophthalmology.*

(11) BOLT Study (24 Month Data)

A 2-Year Prospective Randomized Controlled Trial of Intravitreal Bevacizumab or Laser Therapy (BOLT) in the Management of Diabetic Macular Edema

24-Month Data: Report 3

Ranjan Rajendram, MD, FRCOphth; Samantha Fraser-Bell, PhD, FRANZCO; Andrew Kaines, FRANZCO; Michel Michaelides, MD, FRCOphth; Robin D. Hamilton, DM, FRCOphth; Simona Degli Esposti, MD; Tunde Peto, MD, PhD; Catherine Egan, FRANZCO; Catey Bunce, DSc; Richard David Leslie, MD, FRCP; Philip G. Hykin, MD, FRCOphth

Objective: To report the 2-year outcomes of the BOLT study, a prospective randomized controlled trial evaluating intravitreous bevacizumab and modified Early Treatment Diabetic Retinopathy Study (ETDRS) macular laser therapy (MLT) in patients with persistent clinically significant macular edema (CSME).

Methods: In a 2-year, single-center, randomized controlled trial, 80 patients with center-involving CSME and visual acuity of 20/40 to 20/320 were randomized to receive either bevacizumab or MLT.

Main Outcome Measures: Primary outcome: difference in ETDRS best-corrected visual acuity (BCVA) between arms. Secondary outcomes: mean change in BCVA, proportion gaining at least 15 and at least 10 ETDRS letters, losing fewer than 15 and at least 30 letters, change in central macular thickness, ETDRS retinopathy severity, and safety outcomes.

Results: At 2 years, mean (SD) ETDRS BCVA was 64.4 (13.3) (ETDRS equivalent Snellen fraction: 20/50) in the bevacizumab arm and 54.8 (12.6) (20/80) in the MLT arm ($P=.005$). The bevacizumab arm gained a median of 9 ETDRS letters vs 2.5 letters for MLT ($P=.005$), with a mean gain of 8.6 letters for bevacizumab vs a mean loss of 0.5 letters for MLT. Forty-nine percent of patients gained 10 or more letters ($P=.001$) and 32% gained at least 15 letters ($P=.004$) for bevacizumab vs 7% and 4% for MLT. Percentage who lost fewer than 15 letters in the MLT arm was 86% vs 100% for bevacizumab ($P=.03$). Mean reduction in central macular thickness was 146 µm in the bevacizumab arm vs 118 µm in the MLT arm. The median number of treatments over 24 months was 13 for bevacizumab and 4 for MLT.

Conclusions: This study provides evidence supporting longer-term use of intravitreous bevacizumab for persistent center-involving CSME.

Application to Clinical Practice: Improvements in BCVA and central macular thickness seen with bevacizumab at 1 year were maintained over the second year with a mean of 4 injections.

Trial Registration: eudract.ema.europa.eu Identifier: 2007-000847-89

Arch Ophthalmol. 2012;130(8):972-979.
Published online April 9, 2012.
doi:10.1001/archophthalmol.2012.393

(12) FAME Study

Long-term Benefit of Sustained-Delivery Fluocinolone Acetonide Vitreous Inserts for Diabetic Macular Edema

*Peter A. Campochiaro, MD,[1] David M. Brown, MD,[2] Andrew Pearson, MD,[3] Thomas Ciulla, MD,[4] David Boyer, MD,[5] Frank G. Holz, MD,[6] Michael Tolentino, MD,[7] Amod Gupta, MD,[8] Lilianne Duarte, MD,[9] Steven Madreperla, MD,[10] John Gonder, MD,[11] Barry Kapik, BS,[12] Kathleen Billman, BS,[12] Frances E. Kane, PhD,[12] for the FAME Study Group**

Objective: To assess the efficacy and safety of intravitreal inserts releasing 0.2 μg/day (low dose) or 0.5 μg/day (high dose) fluocinolone acetonide (FA) in patients with diabetic macular edema (DME).

Design: Two parallel, prospective, randomized, sham injection-controlled, double-masked, multicenter clinical trials.

Participants: Subjects with persistent DME despite at least 1 macular laser treatment were randomized 1:2:2 to sham injection (n = 185), low-dose insert (n = 375), or high-dose insert (n = 393).

Methods: Subjects received study drug or sham injection at baseline and after 6 weeks were eligible for rescue laser. Based on retreatment criteria, additional study drug or sham injections could be given after 1 year.

Main Outcome Measures: The primary outcome was the percentage of patients with improvement from baseline best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Trial (ETDRS) letter score of 15 or more at month 24. Secondary outcomes included other parameters of visual function and foveal thickness (FTH).

Results: The percentage of patients with improvement from baseline ETDRS letter score of 15 or more at month 24 was 28.7 and 28.6 in the low- and high-dose insert groups, respectively, compared with 16.2 in the sham group ($P = 0.002$ for each). Benefit occurred for both doses compared with sham at 3 weeks and all subsequent time points. The mean improvement in BCVA letter score between baseline and month 24 was 4.4 and 5.4 in the low- and high-dose groups, respectively, compared with 1.7 in the sham group ($P = 0.02$ and $P = 0.016$). At all time points compared with sham, there was significantly more improvement in FTH. Subjects requiring cataract surgery were more frequent in the insert groups, and their visual benefit was similar to that of subjects who were pseudophakic at baseline. Glaucoma requiring incisional surgery occurred in 3.7%, 7.6%, and 0.5% of the low-dose, high-dose, and sham groups, respectively.

Conclusions: Both low- and high-dose FA inserts significantly improved BCVA in patients with DME over 2 years, and the risk-to-benefit ratio was superior for the low-dose insert. This is the first pharmacologic treatment that can be administered by an outpatient injection to provide substantial benefit in patients with DME for at least 2 years.

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

Ophthalmology 2011;118:626–635

(12) FAME Study

Sustained Delivery Fluocinolone Acetonide Vitreous Inserts Provide Benefit for at Least 3 Years in Patients with Diabetic Macular Edema

*Peter A. Campochiaro, MD,[1] David M. Brown, MD,[2] Andrew Pearson, MD,[3] Sanford Chen, MD,[4] David Boyer, MD,[5] Jose Ruiz-Moreno, MD,[6] Bruce Garretson, MD,[7] Amod Gupta, MD,[8] Seenu M. Hariprasad, MD,[9] Clare Bailey, MD,[10] Elias Reichel, MD,[11] Gisele Soubrane, MD,[12] Barry Kapik, MS,[13] Kathleen Billman, BS,[13] Frances E. Kane, PhD,[13] Kenneth Green, PhD,[13] for the FAME Study Group**

Objective: To assess long-term efficacy and safety of intravitreal inserts releasing 0.2 μg/d (low dose) or 0.5 μg/d (high dose) fluocinolone acetonide (FAc) in patients with diabetic macular edema (DME).

Design: Two randomized, sham injection-controlled, double-masked, multicenter clinical trials.

Participants: Subjects with persistent DME despite ≥1 macular laser treatment were randomized 1:2:2 to sham injection (n = 185), low-dose insert (n = 375), or high-dose insert (n = 393).

Methods: Subjects received study drug or sham injection and after 6 weeks were eligible for rescue laser. Based on retreatment criteria, additional study drug or sham injections could be given after 1 year.

Main Outcome Measures: Percentage of patients with improvement of ≥15 letters from baseline. Secondary outcomes included other parameters of visual function and foveal thickness.

Results: At month 36, the percentage of patients who gained ≥15 in letter score using the last observation carried forward method was 28.7% (low dose) and 27.8% (high dose) in the FAc insert groups compared with 18.9% ($P = 0.018$) in the sham group, and considering only those patients still in the trial at month 36, it was 33.0% (low dose) and 31.9% (high dose) compared with 21.4% in the sham group ($P = 0.030$). Preplanned subgroup analysis demonstrated a doubling of benefit compared with sham injections in patients who reported duration of DME ≥3 years at baseline; the percentage who gained ≥15 in letter score at month 36 was 34.0% (low dose; $P<0.001$) or 28.8% (high dose; $P = 0.002$) compared with 13.4% (sham). An improvement ≥2 steps in the Early Treatment Diabetic Retinopathy Study retinopathy scale occurred in 13.7% (low dose) and 10.1% (high dose) compared with 8.9% in the sham group. Almost all phakic patients in the FAc insert groups developed cataract, but their visual benefit after cataract surgery was similar to that in pseudophakic patients. The incidence of incisional glaucoma surgery at month 36 was 4.8% in the low-dose group and 8.1% in the high-dose insert group.

Conclusions: In patients with DME FAc inserts provide substantial visual benefit for up to 3 years and would provide a valuable addition to the options available for patients with DME.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2012;119:2125–2132

(13) MEAD Study

Three-Year, Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients with Diabetic Macular Edema

David S. Boyer, MD,[1] Young Hee Yoon, MD, PhD,[2] Rubens Belfort, Jr, MD, PhD,[3] Francesco Bandello, MD,[4] Raj K. Maturi, MD,[5] Albert J. Augustin, MD,[6] Xiao-Yan Li, MD,[7] Harry Cui, MS,[7] Yehia Hashad, MD,[7] Scott M. Whitcup, MD,[7] for the Ozurdex MEAD Study Group*

Purpose: To evaluate the safety and efficacy of dexamethasone intravitreal implant (Ozurdex, DEX implant) 0.7 and 0.35 mg in the treatment of patients with diabetic macular edema (DME).

Design: Two randomized, multicenter, masked, sham-controlled, phase III clinical trials with identical protocols were conducted. Data were pooled for analysis.

Participants: Patients (n = 1048) with DME, best-corrected visual acuity (BCVA) of 20/50 to 20/200 Snellen equivalent, and central retinal thickness (CRT) of ≥300 μm by optical coherence tomography.

Methods: Patients were randomized in a 1:1:1 ratio to study treatment with DEX implant 0.7 mg, DEX implant 0.35 mg, or sham procedure and followed for 3 years (or 39 months for patients treated at month 36) at ≤40 scheduled visits. Patients who met retreatment eligibility criteria could be retreated no more often than every 6 months.

Main Outcome Measures: The predefined primary efficacy endpoint for the United States Food and Drug Administration was achievement of ≥15-letter improvement in BCVA from baseline at study end. Safety measures included adverse events and intraocular pressure (IOP).

Results: Mean number of treatments received over 3 years was 4.1, 4.4, and 3.3 with DEX implant 0.7 mg, DEX implant 0.35 mg, and sham, respectively. The percentage of patients with ≥15-letter improvement in BCVA from baseline at study end was greater with DEX implant 0.7 mg (22.2%) and DEX implant 0.35 mg (18.4%) than sham (12.0%; $P \leq 0.018$). Mean average reduction in CRT from baseline was greater with DEX implant 0.7 mg (−111.6 μm) and DEX implant 0.35 mg (−107.9 μm) than sham (−41.9 μm; $P < 0.001$). Rates of cataract-related adverse events in phakic eyes were 67.9%, 64.1%, and 20.4% in the DEX implant 0.7 mg, DEX implant 0.35 mg, and sham groups, respectively. Increases in IOP were usually controlled with medication or no therapy; only 2 patients (0.6%) in the DEX implant 0.7 mg group and 1 (0.3%) in the DEX implant 0.35 mg group required trabeculectomy.

Conclusions: The DEX implant 0.7 mg and 0.35 mg met the primary efficacy endpoint for improvement in BCVA. The safety profile was acceptable and consistent with previous reports. *Ophthalmology 2014;121:1904-1914*

(13) MEAD Study – Subgroup Analysis

Dexamethasone intravitreal implant in previously treated patients with diabetic macular edema: subgroup analysis of the MEAD study

Albert J. Augustin[1*], Baruch D. Kuppermann[2], Paolo Lanzetta[3], Anat Loewenstein[4], Xiao-Yan Li[5], Harry Cui[6], Yehia Hashad[5] and Scott M. Whitcup[7] for the Ozurdex MEAD Study Group

Abstract

Background: Dexamethasone intravitreal implant 0.7 mg (DEX 0.7) was approved for treatment of diabetic macular edema (DME) after demonstration of its efficacy and safety in the MEAD registration trials. We performed subgroup analysis of MEAD study results to evaluate the efficacy and safety of DEX 0.7 treatment in patients with previously treated DME.

Methods: Three-year, randomized, sham-controlled phase 3 study in patients with DME, best-corrected visual acuity (BCVA) of 34–68 Early Treatment Diabetic Retinopathy Study letters (20/200–20/50 Snellen equivalent), and central retinal thickness (CRT) ≥300 μm measured by time-domain optical coherence tomography. Patients were randomized to 1 of 2 doses of DEX (0.7 mg or 0.35 mg), or to sham procedure, with retreatment no more than every 6 months. The primary endpoint was ≥15-letter gain in BCVA at study end. Average change in BCVA and CRT from baseline during the study (area-under-the-curve approach) and adverse events were also evaluated. The present subgroup analysis evaluated outcomes in patients randomized to DEX 0.7 (marketed dose) or sham based on prior treatment for DME at study entry.

Results: Baseline characteristics of previously treated DEX 0.7 ($n = 247$) and sham ($n = 261$) patients were similar. In the previously treated subgroup, mean number of treatments over 3 years was 4.1 for DEX 0.7 and 3.2 for sham, 21.5 % of DEX 0.7 patients versus 11.1 % of sham had ≥15-letter BCVA gain from baseline at study end ($P = 0.002$), mean average BCVA change from baseline was +3.2 letters with DEX 0.7 versus +1.5 letters with sham ($P = 0.024$), and mean average CRT change from baseline was −126.1 μm with DEX 0.7 versus −39.0 μm with sham ($P < 0.001$). Cataract-related adverse events were reported in 70.3 % of baseline phakic patients in the previously treated DEX 0.7 subgroup; vision gains were restored following cataract surgery.

Conclusions: DEX 0.7 significantly improved visual and anatomic outcomes in patients with DME previously treated with laser, intravitreal anti-vascular endothelial growth factor, intravitreal triamcinolone acetonide, or a combination of these therapies. The safety profile of DEX 0.7 in previously treated patients was similar to its safety profile in the total study population.

Trial registration: ClinicalTrials.gov NCT00168337 and NCT00168389, registered 12 September 2005

Keywords: Corticosteroid, Dexamethasone, Diabetic retinopathy, Drug delivery, Implant, Macular edema

BMC Ophthalmology (2015) 15:150

(14) DAVINCI Study

The DA VINCI Study: Phase 2 Primary Results of VEGF Trap-Eye in Patients with Diabetic Macular Edema

Diana V. Do, MD,[1] Ursula Schmidt-Erfurth, MD,[2] Victor H. Gonzalez, MD,[3] Carmelina M. Gordon, MD,[4] Michael Tolentino, MD,[5] Alyson J. Berliner, MD, PhD,[6] Robert Vitti, MD, MBA,[5] Rene Rückert, MD,[7] Rupert Sandbrink, MD, PhD,[7,8] David Stein, BS,[6] Ke Yang, PhD,[6] Karola Beckmann, MSc,[7] Jeff S. Heier, MD[9]

Purpose: To determine whether different doses and dosing regimens of intravitreal vascular endothelial growth factor (VEGF) Trap-Eye are superior to focal/grid photocoagulation in eyes with diabetic macular edema (DME).

Design: Multicenter, randomized, double-masked, phase 2 clinical trial.

Participants: A total of 221 diabetic patients with clinically significant macular edema involving the central macula.

Methods: Patients were assigned to 1 of 5 treatment regimens: 0.5 mg VEGF Trap-Eye every 4 weeks; 2 mg VEGF Trap-Eye every 4 weeks; 2 mg VEGF Trap-Eye for 3 initial monthly doses and then every 8 weeks; 2 mg VEGF Trap-Eye for 3 initial monthly doses and then on an as-needed (PRN) basis; or macular laser photocoagulation. Assessments were completed at baseline and every 4 weeks thereafter.

Main Outcome Measures: Mean change in visual acuity and central retinal thickness (CRT) at 24 weeks.

Results: Patients in the 4 VEGF Trap-Eye groups experienced mean visual acuity benefits ranging from +8.5 to +11.4 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters versus only +2.5 letters in the laser group ($P \leq 0.0085$ for each VEGF Trap-Eye group vs. laser). Gains from baseline of 0+, 10+, and 15+ letters were seen in up to 93%, 64%, and 34% of VEGF Trap-Eye groups versus up to 68%, 32%, and 21% in the laser group, respectively. Mean reductions in CRT in the 4 VEGF Trap-Eye groups ranged from −127.3 to −194.5 μm compared with only −67.9 μm in the laser group ($P = 0.0066$ for each VEGF Trap-Eye group vs. laser). VEGF Trap-Eye was generally well tolerated. Ocular adverse events in patients treated with VEGF Trap-Eye were generally consistent with those seen with other intravitreal anti-VEGF agents.

Conclusions: Intravitreal VEGF Trap-Eye produced a statistically significant and clinically relevant improvement in visual acuity when compared with macular laser photocoagulation in patients with DME.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2011;118:1819–1826

(14) DAVINCI Study

One-Year Outcomes of the DA VINCI Study of VEGF Trap-Eye in Eyes with Diabetic Macular Edema

*Diana V. Do, MD,[1] Quan Dong Nguyen, MD, MSc,[1] David Boyer, MD,[2] Ursula Schmidt-Erfurth, MD,[3] David M. Brown, MD,[4] Robert Vitti, MD,[5] Alyson J. Berliner, MD,[5] Bo Gao, PhD,[5] Oliver Zeitz, MD,[6,7] Rene Ruckert, MD,[6] Thomas Schmelter, PhD,[6] Rupert Sandbrink, MD, PhD,[6,8] Jeff S. Heier, MD,[9] for the DA VINCI Study Group**

Purpose: To compare different doses and dosing regimens of Vascular Endothelial Growth Factor (VEGF) Trap-Eye with laser photocoagulation in eyes with diabetic macular edema (DME).

Design: Randomized, double-masked, multicenter, phase 2 clinical trial.

Participants: Diabetic patients (n = 221) with center-involved DME.

Methods: Participants were assigned randomly to 1 of 5 treatment regimens: VEGF Trap-Eye 0.5 mg every 4 weeks (0.5q4); 2 mg every 4 weeks (2q4); 2 mg every 8 weeks after 3 initial monthly doses (2q8); or 2 mg dosing as needed after 3 initial monthly doses (2PRN), or macular laser photocoagulation.

Main Outcome Measures: The change in best-corrected visual acuity (BCVA) at 24 weeks (the primary end point) and at 52 weeks, proportion of eyes that gained 15 letters or more in Early Treatment of Diabetic Retinopathy Study (ETDRS) BCVA, and mean changes in central retinal thickness (CRT) from baseline.

Results: As previously reported, mean improvements in BCVA in the VEGF Trap-Eye groups at week 24 were 8.6, 11.4, 8.5, and 10.3 letters for 0.5q4, 2q4, 2q8, and 2PRN regimens, respectively, versus 2.5 letters for the laser group ($P \leq 0.0085$ versus laser). Mean improvements in BCVA in the VEGF Trap-Eye groups at week 52 were 11.0, 13.1, 9.7, and 12.0 letters for 0.5q4, 2q4, 2q8, and 2PRN regimens, respectively, versus −1.3 letters for the laser group ($P \leq 0.0001$ versus laser). Proportions of eyes with gains in BCVA of 15 or more ETDRS letters at week 52 in the VEGF Trap-Eye groups were 40.9%, 45.5%, 23.8%, and 42.2% versus 11.4% for laser ($P = 0.0031$, $P = 0.0007$, $P = 0.1608$, and $P = 0.0016$, respectively, versus laser). Mean reductions in CRT in the VEGF Trap-Eye groups at week 52 were −165.4 μm, −227.4 μm, −187.8 μm, and −180.3 μm versus −58.4 μm for laser ($P < 0.0001$ versus laser). Vascular Endothelial Growth Factor Trap-Eye generally was well tolerated. The most frequent ocular adverse events with VEGF Trap-Eye were conjunctival hemorrhage, eye pain, ocular hyperemia, and increased intraocular pressure, whereas common systemic adverse events included hypertension, nausea, and congestive heart failure.

Conclusions: Significant gains in BCVA from baseline achieved at week 24 were maintained or improved at week 52 in all VEGF Trap-Eye groups. Vascular Endothelial Growth Factor Trap-Eye warrants further investigation for the treatment of DME.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. *Ophthalmology 2012;119:1658–1665*

(15) VISTA and VIVID - Study

Intravitreal Aflibercept for Diabetic Macular Edema

Jean-François Korobelnik, MD,[1,2,3] Diana V. Do, MD,[4] Ursula Schmidt-Erfurth, MD,[5] David S. Boyer, MD,[6] Frank G. Holz, MD,[7] Jeffrey S. Heier, MD,[8] Edoardo Midena, MD,[9] Peter K. Kaiser, MD,[10] Hiroko Terasaki, MD,[11] Dennis M. Marcus, MD,[12] Quan D. Nguyen, MD,[4] Glenn J. Jaffe, MD,[13] Jason S. Slakter, MD,[14] Christian Simader, MD,[5] Yuhwen Soo, PhD,[15] Thomas Schmelter, PhD,[16] George D. Yancopoulos, MD, PhD,[15] Neil Stahl, PhD,[15] Robert Vitti, MD,[15] Alyson J. Berliner, MD, PhD,[15] Oliver Zeitz, MD,[16,17] Carola Metzig, MD,[16] David M. Brown, MD[18]

Purpose: A head-to-head comparison was performed between vascular endothelial growth factor blockade and laser for treatment of diabetic macular edema (DME).

Design: Two similarly designed, double-masked, randomized, phase 3 trials, VISTA^{DME} and VIVID^{DME}.

Participants: We included 872 patients (eyes) with type 1 or 2 diabetes mellitus who presented with DME with central involvement.

Methods: Eyes received either intravitreal aflibercept injection (IAI) 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 initial monthly doses (2q8), or macular laser photocoagulation.

Main Outcome Measures: The primary efficacy endpoint was the change from baseline in best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letters at week 52. Secondary efficacy endpoints at week 52 included the proportion of eyes that gained ≥15 letters from baseline and the mean change from baseline in central retinal thickness as determined by optical coherence tomography.

Results: Mean BCVA gains from baseline to week 52 in the IAI 2q4 and 2q8 groups versus the laser group were 12.5 and 10.7 versus 0.2 letters ($P < 0.0001$) in VISTA, and 10.5 and 10.7 versus 1.2 letters ($P < 0.0001$) in VIVID. The corresponding proportions of eyes gaining ≥15 letters were 41.6% and 31.1% versus 7.8% ($P < 0.0001$) in VISTA, and 32.4% and 33.3% versus 9.1% ($P < 0.0001$) in VIVID. Similarly, mean reductions in central retinal thickness were 185.9 and 183.1 versus 73.3 μm ($P < 0.0001$) in VISTA, and 195.0 and 192.4 versus 66.2 μm ($P < 0.0001$) in VIVID. Overall incidences of ocular and nonocular adverse events and serious adverse events, including the Anti-Platelet Trialists' Collaboration–defined arterial thromboembolic events and vascular deaths, were similar across treatment groups.

Conclusions: At week 52, IAI demonstrated significant superiority in functional and anatomic endpoints over laser, with similar efficacy in the 2q4 and 2q8 groups despite the extended dosing interval in the 2q8 group. In general, IAI was well-tolerated. *Ophthalmology 2014;121:2247-2254 © 2014 by the American Academy of Ophthalmology.*

(15) VISTA and VIVID – Study – 100 week results

Intravitreal Aflibercept for Diabetic Macular Edema

100-Week Results From the VISTA and VIVID Studies

David M. Brown, MD,[1] Ursula Schmidt-Erfurth, MD,[2] Diana V. Do, MD,[3] Frank G. Holz, MD,[4] David S. Boyer, MD,[5] Edoardo Midena, MD,[6] Jeffrey S. Heier, MD,[7] Hiroko Terasaki, MD,[8] Peter K. Kaiser, MD,[9] Dennis M. Marcus, MD,[10] Quan D. Nguyen, MD,[3] Glenn J. Jaffe, MD,[11] Jason S. Slakter, MD,[12] Christian Simader, MD,[2] Yuhwen Soo, PhD,[13] Thomas Schmelter, PhD,[14] George D. Yancopoulos, MD, PhD,[13] Neil Stahl, PhD,[13] Robert Vitti, MD,[13] Alyson J. Berliner, MD, PhD,[13] Oliver Zeitz, MD,[14,15] Carola Metzig, MD,[14] Jean-François Korobelnik, MD[16,17,18]

Purpose: To compare efficacy and safety of 2 dosing regimens of intravitreal aflibercept injection (IAI) with macular laser photocoagulation for diabetic macular edema (DME).

Design: Two similarly designed, randomized, phase 3 trials, VISTA^{DME} and VIVID^{DME}.

Participants: Patients (eyes; n=872) with type 1 or 2 diabetes mellitus who had DME with central involvement.

Methods: Eyes received IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 monthly doses (2q8), or laser control.

Main Outcome Measures: The primary end point was mean change from baseline in best-corrected visual acuity (BCVA) at week 52. This report presents the 100-week results including mean change from baseline in BCVA, proportion of eyes that gained ≥15 letters, and proportion of eyes with a ≥2-step improvement in the Diabetic Retinopathy Severity Scale (DRSS) score.

Results: Mean BCVA gain from baseline to week 100 with IAI 2q4, IAI 2q8, and laser control was 11.5, 11.1, and 0.9 letters ($P < 0.0001$) in VISTA and 11.4, 9.4, and 0.7 letters ($P < 0.0001$) in VIVID, respectively. The proportion of eyes that gained ≥15 letters from baseline at week 100 was 38.3%, 33.1%, and 13.0% ($P < 0.0001$) in VISTA and 38.2%, 31.1%, and 12.1% ($P \leq 0.0001$) in VIVID. The proportion of eyes that lost ≥15 letters at week 100 was 3.2%, 0.7%, and 9.7% ($P \leq 0.0220$) in VISTA and 2.2%, 1.5%, and 12.9% ($P \leq 0.0008$) in VIVID. Significantly more eyes in the IAI 2q4 and 2q8 groups versus those in the laser control group had a ≥2 step improvement in the DRSS score in both VISTA (37.0% and 37.1% vs. 15.6%; $P < 0.0001$) and VIVID (29.3% and 32.6% vs. 8.2%; $P \leq 0.0004$). In an integrated safety analysis, the most frequent serious ocular adverse event was cataract (2.4%, 1.0%, and 0.3% for 2q4, 2q8, and control).

Conclusions: In both VISTA and VIVID, the 52-week visual and anatomic superiority of IAI over laser control was sustained through week 100, with similar efficacy in the 2q4 and 2q8 groups. Safety in these studies was consistent with the known safety profile of IAI. *Ophthalmology 2015;122:2044-2052 © 2015 by the American Academy of Ophthalmology.*

III. Vitreoretinal Surgery Trials

(1) DRCR Protocol D

Vitrectomy Outcomes in Eyes with Diabetic Macular Edema and Vitreomacular Traction

Diabetic Retinopathy Clinical Research Network Writing Committee on behalf of the DRCR.net*

Purpose: To evaluate vitrectomy for diabetic macular edema (DME) in eyes with at least moderate vision loss and vitreomacular traction.

Design: Prospective cohort study.

Participants: The primary cohort included 87 eyes with DME and vitreomacular traction based on investigator's evaluation, visual acuity 20/63–20/400, optical coherence tomography (OCT) central subfield >300 microns and no concomitant cataract extraction at the time of vitrectomy.

Methods: Surgery was performed according to the investigator's usual routine. Follow-up visits were performed after 3 months, 6 months (primary end point), and 1 year.

Main Outcome Measures: Visual acuity, OCT retinal thickening, and operative complications.

Results: At baseline, median visual acuity in the 87 eyes was 20/100 and median OCT thickness was 491 microns. During vitrectomy, additional procedures included epiretinal membrane peeling in 61%, internal limiting membrane peeling in 54%, panretinal photocoagulation in 40%, and injection of corticosteroids at the close of the procedure in 64%. At 6 months, median OCT central subfield thickness decreased by 160 microns, with 43% having central subfield thickness <250 microns and 68% having at least a 50% reduction in thickening. Visual acuity improved by ≥10 letters in 38% (95% confidence interval, 28%–49%) and deteriorated by ≥10 letters in 22% (95% confidence interval, 13%–31%). Postoperative complications through 6 months included vitreous hemorrhage (5 eyes), elevated intraocular pressure requiring treatment (7 eyes), retinal detachment (3 eyes), and endophthalmitis (1 eye). Few changes in results were noted between 6 months and 1 year.

Conclusions: After vitrectomy performed for DME and vitreomacular traction, retinal thickening was reduced in most eyes. Between 28% and 49% of eyes with characteristics similar to those included in this study are likely to have improvement of visual acuity, whereas between 13% and 31% are likely to have worsening. The operative complication rate is low and similar to what has been reported for this procedure. These data provide estimates of surgical outcomes and serve as a reference for future studies that might consider vitrectomy for DME in eyes with at least moderate vision loss and vitreomacular traction.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. *Ophthalmology 2010;117:1087–1093*

(1) DRCR Protocol D

FACTORS ASSOCIATED WITH VISUAL ACUITY OUTCOMES AFTER VITRECTOMY FOR DIABETIC MACULAR EDEMA

Diabetic Retinopathy Clinical Research Network

CHRISTINA J. FLAXEL, MD,* ALLISON R. EDWARDS, MS,† LLOYD PAUL AIELLO, MD, PHD,‡ PAUL G. ARRIGG, MD,§ ROY W. BECK, MD, PHD,† NEIL M. BRESSLER, MD,¶ SUSAN B. BRESSLER, MD,¶ FREDERICK L. FERRIS, III, MD,** SHAILESH K. GUPTA, MD,†† JULIA A. HALLER, MD,‡‡ HOWARD S. LAZARUS, MD,§§ HAIJING QIN, MS†

Purpose: To evaluate factors ¶associated with favorable outcomes after vitrectomy for diabetic macular edema.

Methods: Data were collected prospectively on 241 eyes undergoing vitrectomy for diabetic macular edema. Multivariate models were used to evaluate associations of 20 preoperative and intraoperative factors with 6-month outcomes of visual acuity and retinal thickness.

Results: Median central subfield thickness decreased from 412 μm to 278 μm at 6 months, but median visual acuity remained unchanged (20/80, Snellen equivalent). Greater visual acuity improvement occurred in eyes with worse baseline acuity ($P < 0.001$) and in eyes in which an epiretinal membrane was removed ($P = 0.006$). Greater reduction in central subfield thickness occurred with worse baseline visual acuity ($P < 0.001$), greater preoperative retinal thickness ($P = 0.001$), removal of internal limiting membrane ($P = 0.003$), and optical coherence tomography evidence of vitreoretinal abnormalities ($P = 0.006$). No associations with clinician's preoperative assessments of the posterior vitreous were identified.

Conclusion: These results suggest that the removal of epiretinal membranes may favorably affect visual outcome after vitrectomy. Preoperative presence of vitreoretinal abnormalities appeared to be associated with somewhat greater reductions in retinal thickness but not with visual acuity outcome. These results may be useful for future studies evaluating vitrectomy for diabetic macular edema.

RETINA 30:1488–1495, 2010

(2) DRVS

Early Vitrectomy for Severe Vitreous Hemorrhage in Diabetic Retinopathy

Two-Year Results of a Randomized Trial
Diabetic Retinopathy Vitrectomy Study Report 2

The Diabetic Retinopathy Vitrectomy Study Research Group

Arch Ophthalmol. 1985 Nov;103(11):1644-52.

Abstract

Six hundred sixteen eyes with recent severe diabetic vitreous hemorrhage reducing visual acuity to 5/200 or less for at least one month were randomly assigned to either early vitrectomy or deferral of vitrectomy for one year. After two years of follow-up, 25% of the early vitrectomy group had visual acuity of 10/20 or better compared with 15% in the deferral group (P = .01). In patients with Type I diabetes, who were on the average younger and had more-severe proliferative retinopathy, there was a clear-cut advantage for early vitrectomy, as reflected in the percentage of eyes recovering visual acuity of 10/20 or better (36% vs 12% in the deferral group, P = .0001). No such advantage was found in the Type II diabetes group (16% in the early group vs 18% in the deferral group), but evidence that this advantage differed by diabetes type was of borderline significance.

(3) ETDRS - Report 17

Ophthalmology. 1992 Sep;99(9):1351-7.

Pars plana vitrectomy in the Early Treatment Diabetic Retinopathy Study. ETDRS report number 17. The Early Treatment Diabetic Retinopathy Study Research Group.

Flynn HW Jr[1], Chew EY, Simons BD, Barton FB, Remaley NA, Ferris FL 3rd.

Abstract

BACKGROUND:
The Early Treatment Diabetic Retinopathy Study (ETDRS) enrolled 3711 patients with mild-to-severe nonproliferative or early proliferative diabetic retinopathy in both eyes. Patients were randomly assigned to aspirin 650 mg/day or placebo. One eye of each patient was assigned randomly to early photocoagulation and the other to deferral of photocoagulation. Follow-up examinations were scheduled at least every 4 months, and photocoagulation was initiated in eyes assigned to deferral as soon as high-risk proliferative retinopathy was detected. Aspirin was not found to have an effect on retinopathy progression or rates of vitreous hemorrhage. The risk of a combined end point, severe visual loss or vitrectomy, was low in eyes assigned to deferral (6% at 5 years) and was reduced by early photocoagulation (4% at 5 years). Vitrectomy was carried out in 208 patients during the 9 years of the study. This report presents baseline and previtrectomy characteristics and visual outcome in these patients.

METHODS:
Information collected at baseline and during follow-up as part of the ETDRS protocol was supplemented by review of clinic charts for visual acuity and ocular status immediately before vitrectomy.

RESULTS:
Vitrectomy was performed in 208 (5.6%) of the 3711 patients (243 eyes) enrolled in the ETDRS. The 5-year vitrectomy rates for eyes grouped by their initial photocoagulation assignment were as follows: 2.1% in the early full scatter photocoagulation group, 2.5% in the early mild scatter group, and 4.0% in the deferral group. The 5-year rates of vitrectomy (in one or both eyes) were 5.4% in patients assigned to aspirin and 5.2% in patients assigned to a placebo. The indications for vitrectomy were either vitreous hemorrhage (53.9%) or retinal detachment with or without vitreous hemorrhage (46.1%). Before vitrectomy, visual acuity was 5/200 or worse in 66.7% of eyes and better than 20/100 in 6.2%. One year after vitrectomy, the visual acuity was 20/100 or better in 47.6% of eyes, including 24.0% with visual acuity of 20/40 or better.

CONCLUSIONS:
With frequent follow-up examinations and timely scatter (panretinal) photocoagulation, the 5-year cumulative rate of pars plana vitrectomy in ETDRS patients was 5.3%. Aspirin use did not influence the rate of vitrectomy.

IV. Medical Management Trials

(1) DCCT study

The New England
Journal of Medicine

Volume 329 SEPTEMBER 30, 1993 Number 14

THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG-TERM COMPLICATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP*

Abstract *Background.* Long-term microvascular and neurologic complications cause major morbidity and mortality in patients with insulin-dependent diabetes mellitus (IDDM). We examined whether intensive treatment with the goal of maintaining blood glucose concentrations close to the normal range could decrease the frequency and severity of these complications.

Methods. A total of 1441 patients with IDDM — 726 with no retinopathy at base line (the primary-prevention cohort) and 715 with mild retinopathy (the secondary-intervention cohort) were randomly assigned to intensive therapy administered either with an external insulin pump or by three or more daily insulin injections and guided by frequent blood glucose monitoring or to conventional therapy with one or two daily insulin injections. The patients were followed for a mean of 6.5 years, and the appearance and progression of retinopathy and other complications were assessed regularly.

Results. In the primary-prevention cohort, intensive therapy reduced the adjusted mean risk for the development of retinopathy by 76 percent (95 percent confidence interval, 62 to 85 percent), as compared with conventional therapy. In the secondary-intervention cohort, intensive therapy slowed the progression of retinopathy by 54 percent (95 percent confidence interval, 39 to 66 percent) and reduced the development of proliferative or severe nonproliferative retinopathy by 47 percent (95 percent confidence interval, 14 to 67 percent). In the two cohorts combined, intensive therapy reduced the occurrence of microalbuminuria (urinary albumin excretion of ≥40 mg per 24 hours) by 39 percent (95 percent confidence interval, 21 to 52 percent), that of albuminuria (urinary albumin excretion of ≥300 mg per 24 hours) by 54 percent (95 percent confidence interval, 19 to 74 percent), and that of clinical neuropathy by 60 percent (95 percent confidence interval, 38 to 74 percent). The chief adverse event associated with intensive therapy was a two-to-threefold increase in severe hypoglycemia.

Conclusions. Intensive therapy effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy, and neuropathy in patients with IDDM. (N Engl J Med 1993;329:977-86.)

(1) DCCT/EDIC Study

Intensive Diabetes Therapy and Ocular Surgery in Type 1 Diabetes

The DCCT/EDIC Research Group*

N Engl J Med. 2015 Apr 30;372(18):1722-33.

ABSTRACT

BACKGROUND

The Diabetes Control and Complications Trial (DCCT) showed a beneficial effect of 6.5 years of intensive glycemic control on retinopathy in patients with type 1 diabetes.

METHODS

Between 1983 and 1989, a total of 1441 patients with type 1 diabetes in the DCCT were randomly assigned to receive either intensive diabetes therapy or conventional therapy aimed at preventing hyperglycemic symptoms. They were treated and followed until 1993. Subsequently, 1375 of these patients were followed in the observational Epidemiology of Diabetes Interventions and Complications (EDIC) study. The self-reported history of ocular surgical procedures was obtained annually. We evaluated the effect of intensive therapy as compared with conventional therapy on the incidence and cost of ocular surgery during these two studies.

RESULTS

Over a median follow-up of 23 years, 130 ocular operations were performed in 63 of 711 patients assigned to intensive therapy (8.9%) and 189 ocular operations in 98 of 730 patients assigned to conventional therapy (13.4%) (P<0.001). After adjustment for DCCT baseline factors, intensive therapy was associated with a reduction in the risk of any diabetes-related ocular surgery by 48% (95% confidence interval [CI], 29 to 63; P<0.001) and a reduction in the risk of all such ocular procedures by 37% (95% CI, 12 to 55; P=0.01). Forty-two patients who received intensive therapy and 61 who received conventional therapy underwent cataract extraction (adjusted risk reduction with intensive therapy, 48%; 95% CI, 23 to 65; P=0.002); 29 patients who received intensive therapy and 50 who received conventional therapy underwent vitrectomy, retinal-detachment surgery, or both (adjusted risk reduction, 45%; 95% CI, 12 to 66; P=0.01). The costs of surgery were 32% lower in the intensive-therapy group. The beneficial effects of intensive therapy were fully attenuated after adjustment for mean glycated hemoglobin levels over the entire follow-up.

CONCLUSIONS

Intensive therapy in patients with type 1 diabetes was associated with a substantial reduction in the long-term risk of ocular surgery. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; DCCT/EDIC ClinicalTrials.gov numbers, NCT00360893 and NCT00360815.)

(2) UKPDS study

Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study

Irene M Stratton, Amanda I Adler, H Andrew W Neil, David R Matthews, Susan E Manley, Carole A Cull, David Hadden, Robert C Turner, Rury R Holman on behalf of the UK Prospective Diabetes Study Group

BMJ. 2000 Aug 12;321(7258):405-12.

Abstract

OBJECTIVE: To determine the relation between exposure to glycaemia over time and the risk of macrovascular or microvascular complications in patients with type 2 diabetes.

DESIGN: Prospective observational study.

SETTING: 23 hospital based clinics in England, Scotland, and Northern Ireland.

PARTICIPANTS: 4585 white, Asian Indian, and Afro-Caribbean UKPDS patients, whether randomised or not to treatment, were included in analyses of incidence; of these, 3642 were included in analyses of relative risk.

OUTCOME MEASURES: Primary predefined aggregate clinical outcomes: any end point or deaths related to diabetes and all cause mortality. Secondary aggregate outcomes: myocardial infarction, stroke, amputation (including death from peripheral vascular disease), and microvascular disease (predominantly retinal photo-coagulation). Single end points: non-fatal heart failure and cataract extraction. Risk reduction associated with a 1% reduction in updated mean HbA(1c) adjusted for possible confounders at diagnosis of diabetes.

RESULTS: The incidence of clinical complications was significantly associated with glycaemia. Each 1% reduction in updated mean HbA(1c) was associated with reductions in risk of 21% for any end point related to diabetes (95% confidence interval 17% to 24%, P<0.0001), 21% for deaths related to diabetes (15% to 27%, P<0.0001), 14% for myocardial infarction (8% to 21%, P<0.0001), and 37% for microvascular complications (33% to 41%, P<0.0001). No threshold of risk was observed for any end point.

CONCLUSIONS: In patients with type 2 diabetes the risk of diabetic complications was strongly associated with previous hyperglycaemia. Any reduction in HbA(1c) is likely to reduce the risk of complications, with the lowest risk being in those with HbA(1c) values in the normal range (<6.0%).

(3) FIELD study

Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial

*A C Keech, P Mitchell, P A Summanen, J O'Day, T M E Davis, M S Moffitt, M-R Taskinen, R J Simes, D Tse, E Williamson, A Merrifield, L T Laatikainen, M C d'Emden, D C Crimet, R L O'Connell, P G Colman, for the FIELD study investigators**

Lancet. 2007 Nov 17;370(9600):1687-97.

Summary

Background Laser treatment for diabetic retinopathy is often associated with visual field reduction and other ocular side-effects. Our aim was to assess whether long-term lipid-lowering therapy with fenofibrate could reduce the progression of retinopathy and the need for laser treatment in patients with type 2 diabetes mellitus.

Methods The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a multinational randomised trial of 9795 patients aged 50–75 years with type 2 diabetes mellitus. Eligible patients were randomly assigned to receive fenofibrate 200 mg/day (n=4895) or matching placebo (n=4900). At each clinic visit, information concerning laser treatment for diabetic retinopathy—a prespecified tertiary endpoint of the main study—was gathered. Adjudication by ophthalmologists masked to treatment allocation defined instances of laser treatment for macular oedema, proliferative retinopathy, or other eye conditions. In a substudy of 1012 patients, standardised retinal photography was done and photographs graded with Early Treatment Diabetic Retinopathy Study (ETDRS) criteria to determine the cumulative incidence of diabetic retinopathy and its component lesions. Analyses were by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN64783481.

Findings Laser treatment was needed more frequently in participants with poorer glycaemic or blood pressure control than in those with good control of these factors, and in those with a greater burden of clinical microvascular disease, but the need for such treatment was not affected by plasma lipid concentrations. The requirement for first laser treatment for all retinopathy was significantly lower in the fenofibrate group than in the placebo group (164 [3·4%] patients on fenofibrate *vs* 238 [4·9%] on placebo; hazard ratio [HR] 0·69, 95% CI 0·56–0·84; p=0·0002; absolute risk reduction 1·5% [0·7–2·3]). In the ophthalmology substudy, the primary endpoint of 2-step progression of retinopathy grade did not differ significantly between the two groups overall (46 [9·6%] patients on fenofibrate *vs* 57 [12·3%] on placebo; p=0·19) or in the subset of patients without pre-existing retinopathy (43 [11·4%] *vs* 43 [11·7%]; p=0·87). By contrast, in patients with pre-existing retinopathy, significantly fewer patients on fenofibrate had a 2-step progression than did those on placebo (three [3·1%] patients *vs* 14 [14·6%]; p=0·004). An exploratory composite endpoint of 2-step progression of retinopathy grade, macular oedema, or laser treatments was significantly lower in the fenofibrate group than in the placebo group (HR 0·66, 95% CI 0·47–0·94; p=0·022).

Interpretation Treatment with fenofibrate in individuals with type 2 diabetes mellitus reduces the need for laser treatment for diabetic retinopathy, although the mechanism of this effect does not seem to be related to plasma concentrations of lipids.

(4) ACCORD

N Engl J Med. 2010 Jul 15;363(3):233-44. doi: 10.1056/NEJMoa1001288. Epub 2010 Jun 29.

Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes

The ACCORD Study Group and ACCORD Eye Study Group*

ABSTRACT

BACKGROUND

We investigated whether intensive glycemic control, combination therapy for dyslipidemia, and intensive blood-pressure control would limit the progression of diabetic retinopathy in persons with type 2 diabetes. Previous data suggest that these systemic factors may be important in the development and progression of diabetic retinopathy.

METHODS

In a randomized trial, we enrolled 10,251 participants with type 2 diabetes who were at high risk for cardiovascular disease to receive either intensive or standard treatment for glycemia (target glycated hemoglobin level, <6.0% or 7.0 to 7.9%, respectively) and also for dyslipidemia (160 mg daily of fenofibrate plus simvastatin or placebo plus simvastatin) or for systolic blood-pressure control (target, <120 or <140 mm Hg). A subgroup of 2856 participants was evaluated for the effects of these interventions at 4 years on the progression of diabetic retinopathy by 3 or more steps on the Early Treatment Diabetic Retinopathy Study Severity Scale (as assessed from seven-field stereoscopic fundus photographs, with 17 possible steps and a higher number of steps indicating greater severity) or the development of diabetic retinopathy necessitating laser photocoagulation or vitrectomy.

RESULTS

At 4 years, the rates of progression of diabetic retinopathy were 7.3% with intensive glycemia treatment, versus 10.4% with standard therapy (adjusted odds ratio, 0.67; 95% confidence interval [CI], 0.51 to 0.87; P=0.003); 6.5% with fenofibrate for intensive dyslipidemia therapy, versus 10.2% with placebo (adjusted odds ratio, 0.60; 95% CI, 0.42 to 0.87; P=0.006); and 10.4% with intensive blood-pressure therapy, versus 8.8% with standard therapy (adjusted odds ratio, 1.23; 95% CI, 0.84 to 1.79; P=0.29).

CONCLUSIONS

Intensive glycemic control and intensive combination treatment of dyslipidemia, but not intensive blood-pressure control, reduced the rate of progression of diabetic retinopathy. (Funded by the National Heart, Lung, and Blood Institute and others; ClinicalTrials.gov numbers, NCT00000620 for the ACCORD study and NCT00542178 for the ACCORD Eye study.)

(4) ACCORD

Diabetic Retinopathy, Its Progression, and Incident Cardiovascular Events in the ACCORD Trial

HERTZEL C. GERSTEIN, MD, MSC[1]
WALTER T. AMBROSIUS, PHD[2]
RONALD DANIS, MD[3]
FARAMARZ ISMAIL-BEIGI, MD, PHD[4]
WILLIAM CUSHMAN, MD[5]
JORGE CALLES, MD[6]
MARYANN BANERJI, MD[7]
ULRICH SCHUBART, MD[8]
EMILY Y. CHEW, MD[9]
FOR THE ACCORD STUDY GROUP

OBJECTIVE—Both the presence of diabetic retinopathy and its severity are significantly associated with future cardiovascular (CV) events. Whether its progression is also linked to incident CV outcomes hasn't been assessed.

RESEARCH DESIGN AND METHODS—The relationship between retinopathy, its 4-year progression, and CV outcomes (CV death or nonfatal myocardial infarction or stroke) was analyzed in participants in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial who also participated in the ACCORD Eye Study. Retinopathy was classified as either none, mild, moderate, or severe, and worsening was classified as a <2-step, 2–3-step, or >3-step change (that included incident laser therapy or vitrectomy).

RESULTS—Participants (n = 3,433) of mean age 61 years had baseline retinal photographs (seven stereoscopic fields). Compared with no retinopathy, the adjusted HRs (95% CI) for the CV outcome rose from 1.49 (1.12–1.97) for mild retinopathy to 2.35 (1.47–3.76) for severe retinopathy. A subset of 2,856 was evaluated for progression of diabetic retinopathy at 4 years. The hazard of the primary outcome increased by 38% (1.38 [1.10–1.74]) for every category of change in retinopathy severity. Additional adjustment for the baseline and follow-up levels of A1C, systolic blood pressure, and lipids either individually or together rendered the relationships between worsening and CV outcomes nonsignificant.

CONCLUSIONS—Both the severity of retinopathy and its progression are determinants of incident CV outcomes. The retina may provide an anatomical index of the effect of metabolic and hemodynamic factors on future CV outcomes.

Diabetes Care 36:1266–1271, 2013

Assessing the Effect of Personalized Diabetes Risk Assessments During Ophthalmologic Visits on Glycemic Control

A Randomized Clinical Trial

Lloyd Paul Aiello, MD, PhD; Allison R. Ayala, MS; Andrew N. Antoszyk, MD; Bambi Arnold-Bush, MPH; Carl Baker, MD; Neil M. Bressler, MD; Michael J. Elman, MD; Adam R. Glassman, MS; Lee M. Jampol, MD; Michele Melia, ScM; Jared Nielsen, MD; Howard A. Wolpert, MD; for the Diabetic Retinopathy Clinical Research Network

IMPORTANCE Optimization of glycemic control is critical to reduce the number of diabetes mellitus–related complications, but long-term success is challenging. Although vision loss is among the greatest fears of individuals with diabetes, comprehensive personalized diabetes education and risk assessments are not consistently used in ophthalmologic settings.

OBJECTIVE To determine whether the point-of-care measurement of hemoglobin A_{1c} (HbA_{1c}) and personalized diabetes risk assessments performed during retinal ophthalmologic visits improve glycemic control as assessed by HbA_{1c} level.

DESIGN, SETTING, AND PARTICIPANTS Ophthalmologist office–based randomized, multicenter clinical trial in which investigators from 42 sites were randomly assigned to provide either a study-prescribed augmented diabetes assessment and education or the usual care. Adults with type 1 or 2 diabetes enrolled into 2 cohorts: those with a more-frequent-than-annual follow-up (502 control participants and 488 intervention participants) and those with an annual follow-up (368 control participants and 388 intervention participants). Enrollment was from April 2011 through January 2013.

INTERVENTIONS Point-of-care measurements of HbA_{1c}, blood pressure, and retinopathy severity; an individualized estimate of the risk of retinopathy progression derived from the findings from ophthalmologic visits; structured comparison and review of past and current clinical findings; and structured education with immediate assessment and feedback regarding participant's understanding. These interventions were performed at enrollment and at routine ophthalmic follow-up visits scheduled at least 12 weeks apart.

MAIN OUTCOMES AND MEASURES Mean change in HbA_{1c} level from baseline to 1-year follow-up. Secondary outcomes included body mass index, blood pressure, and responses to diabetes self-management practices and attitudes surveys.

RESULTS In the cohort with more-frequent-than-annual follow-ups, the mean (SD) change in HbA_{1c} level at 1 year was −0.1% (1.5%) in the control group and −0.3% (1.4%) in the intervention group (adjusted mean difference, −0.09% [95% CI, −0.29% to 0.12%]; $P = .35$). In the cohort with annual follow-ups, the mean (SD) change in HbA_{1c} level was 0.0% (1.1%) in the control group and −0.1% (1.6%) in the intervention group (mean difference, −0.05% [95% CI, −0.27% to 0.18%]; $P = .63$). Results were similar for all secondary outcomes.

CONCLUSIONS AND RELEVANCE Long-term optimization of glycemic control is not achieved by a majority of individuals with diabetes. The addition of personalized education and risk assessment during retinal ophthalmologic visits did not result in a reduction in HbA_{1c} level compared with usual care over 1 year. These data suggest that optimizing glycemic control remains a substantive challenge requiring interventional paradigms other than those examined in our study.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01323348

JAMA Ophthalmol. 2015;133(8):888-896.

Diabetic Retinopathy Clinical Research Network (DRCRnet)

1. Browning DJ, Glassman AR, Aiello LP, Bressler NM, Bressler SB, Danis RP, Davis MD, Ferris FL, Huang SS, Kaiser PK, Kollman C, Sadda S, Scott IU, Qin H; Diabetic Retinopathy Clinical Research Network. **Optical coherence tomography measurements and analysis methods in optical coherence tomography studies of diabetic macular edema.** Ophthalmology.2008 Aug;115(8):1366-71, 1371.e1 (Published).

2. Browning DJ, Altaweel MM, Bressler NM, Bressler SB, Scott IU; Diabetic Retinopathy Clinical Research Network. **Diabetic macular edema: what is focal and what is diffuse?.** Am J Ophthalmol.2008 Nov;146 (5):649-55.e1-6. (Published).

3. Glassman AR, Beck RW, Browning DJ, Danis RP, Kollman C; Diabetic Retinopathy Clinical Research Network Study Group. **Comparison of optical coherence tomography in diabetic macular edema, with and without reading center manual grading from a clinical trials perspective.** Invest Ophthalmol Vis Sci.2009 Feb;50 (2):560-6 (Published).

4. Sun JK, Aiello LP, Stockman M, Cavallerano JD, Kopple A, Eagan S, Qin H, Kollman C, Beck RW, Glassman AR; Diabetic Retinopathy Clinical Research Network. **Effects of dilation on Electronic-ETDRS Visual Acuity in diabetic patients.** Invest Ophthalmol Vis Sci.2009 Apr;50(4):1580-4. (Published).

5. Bhavsar AR, Googe JM Jr, Stockdale CR, Bressler NM, Brucker AJ, Elman MJ, Glassman AR; Diabetic Retinopathy Clinical Research Network. **The Risk of Endophthalmitis Following Intravitreal Injection in the DRCR.net Laser-Ranibizumab-Triamcinolone Clinical Trials.** Arch Ophthalmol. 2009 Dec;127(12):1581-3 (Published).

6. Ferris FL, Miller KM, Glassman AR, Beck RW; Diabetic Retinopathy Clinical Research Network. **A proposed method of logarithmic transformation of ocular coherence tomography data for use in clinical research.** Ophthalmology 2010 Aug;117:1512–1516 (Published).

7. Sun JK, Aiello LP, Cavallerano JD, Stockman M, Miller KM, Qin H, Beck RW, Glassman AR; Diabetic Retinopathy Clinical Research Network. **Visual acuity testing using autorefraction or pinhole as compared with manual DRCR protocol refraction in individuals with diabetes.** Ophthalmology.2011 Mar;118:537–542 (Published).

8. Gangaputra S, Almukhtar T, Glassman AR, Aiello LP, Bressler NM, Bressler SB, Danis RP, Davis MD, for the Diabetic Retinopathy Clinical Research Network. **Comparison of Film and Digital Fundus Photographs in Eyes of Individuals with Diabetes Mellitus.** IOVS 2011 Aug;52:6168-73 (Published).

9. Bhavsar AR, Stockdale CR, Ferris FL III, Brucker AJ, Bressler NM, Glassman AR, for the Diabetic Retinopathy Clinical Research. **Update on Risk of Endophthalmitis After Intravitreal Drug Injections and Potential Impact of Elimination of Topical Antibiotics.** Arch Ophthalmol. 2012 Jun;130(6):809-810 (Published).

10.Bressler SB, Almukhtar T, Bhorade A, Bressler NM, Glassman AR, Huang S, Jampol LM, Kim JE, Melia M, for the Diabetic Retinopathy Clinical Research Network. **Repeated Intravitreous Ranibizumab**

Injections for Diabetic Macular Edema and the Risk of Sustained IOP Elevation or Ocular Hypotensive Treatment. JAMA Ophthalmology. 2014 *(Submitted for Publication)*. (*Manuscript*)

11.Bressler SB, Melia M, Glassman AR, Almukhtar T, Jampol LM, Shami M, Berger BB, Bressler NM, for the Diabetic Retinopathy Clinical Research Network. **Ranibizumab plus prompt or deferred laser for diabetic macular edema in eyes with vitrectomy prior to anti-vascular endothelial growth factor therapy.** Retina. 2014 *(Submitted for Publication)*.

12.Jampol LM, Bressler NM, Glassman AR. **Revolution to a new standard treatment of diabetic macular edema.** JAMA. 2014 Jun 11;311(22):2269-70 (Published).

Protocol A - Laser Photocoagulation for Diabetic Macular Edema:

1. Diabetic Retinopathy Clinical Research Network, Browning DJ, Glassman AR, Aiello LP, Beck RW, Brown DM, Fong DS, Bressler NM, Danis RP, Kinyoun JL, Nguyen QD, Bhavsar AR, Gottlieb J, Pieramici DJ, Rauser ME, Apte RS, Lim JI, Miskala PH. **Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema.** Ophthalmology.2007 Mar;114(3):525-36 (Published).

2. Writing Committee for the Diabetic Retinopathy Clinical Research Network, Fong DS, Strauber SF, Aiello LP, Beck RW, Callanan DG, Danis RP, Davis MD, Feman SS, Ferris F, Friedman SM, Garcia CA, Glassman AR, Han DP, Le D, Kollman C, Lauer AK, Recchia FM, Solomon SD. **Comparison of the modified Early Treatment Diabetic Retinopathy Study and mild macular grid laser photocoagulation strategies for diabetic macular edema.** Arch Ophthalmol.2007 Apr;125(4):469-80 (Published).

3. Davis MD, Bressler SB, Aiello LP, Bressler NM, Browning DJ, Flaxel CJ, Fong DS, Foster WJ, Glassman AR, Hartnett ME, Kollman C, Li HK, Qin H, Scott IU; Diabetic Retinopathy Clinical Research Network Study Group. **Comparison of time-domain OCT and fundus photographic assessments of retinal thickening in eyes with diabetic macular edema.** Invest Ophthalmol Vis Sci.2008 May;49(5):1745-52 (Published).

4. Browning DJ, Apte RS, Bressler SB, Chalam KV, Danis RP, Davis MD, Kollman C, Qin H, Sadda S, Scott IU; Diabetic Retinopathy Clinical Research Network. **Association of the extent of diabetic macular edema as assessed by optical coherence tomography with visual acuity and retinal outcome variables.** Retina.2009 Mar;29(3):300-5 (Published).

5. Scott IU, Danis RP, Bressler SB, Bressler NM, Browning DJ, Qin H; Diabetic Retinopathy Clinical Research Network. **Effect of focal/grid photocoagulation on visual acuity and retinal thickening in eyes with non- center-involved diabetic macular edema.** Retina 2009 May;29(5):613-7 (Published).

6. Danis RP, Scott IU, Qin H, Altaweel MM, Bressler NM, Bressler SB, Browning DJ, Kollman C; Diabetic Retinopathy Clinical Research Network. **Association of fluorescein angiographic features with visual acuity and with OCT and stereoscopic color fundus photographic features of DME in a randomized clinical trial.** Retina.2010 Dec;30(10):1627-37 (Published).

Protocol B - Intravitreal Triamcinolone Acetonide versus Laser Study:

1. Bhavsar AR, Ip MS, Glassman AR; DRCRnet and the SCORE Study Groups. **The risk of endophthalmitis following intravitreal triamcinolone injection in the DRCRnet and SCORE clinical trials.** Am J Ophthalmol.2007 Sep;144(3):454-6 (Published).

2. Ip MS, Bressler SB, Antoszyk AN, Flaxel CJ, Kim JE, Friedman SM, Qin H; Diabetic Retinopathy Clinical Research Network. **A randomized trial comparing intravitreal triamcinolone and focal/grid photocoagulation for diabetic macular edema: baseline features.** Retina.2008 Jul-Aug;28(7):919-30 (Published).

3. Diabetic Retinopathy Clinical Research Network. **A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema.** Ophthalmology.2008 Sep;115 (9):1447-9.e1-10 (Published).

4. Diabetic Retinopathy Clinical Research Network (DRCR.net), Beck RW, Edwards AR, Aiello LP, Bressler NM, Ferris F, Glassman AR, Hartnett E, Ip MS, Kim JE, Kollman C. **Three-year follow up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema.** Arch Ophthalmol.2009 Mar;127(3):245-51 (Published).

5. Bressler NM, Edwards AR, Beck RW, Flaxel CJ, Glassman AR, Ip MS, Kollman C, Kuppermann BD, Stone TW; Diabetic Retinopathy Clinical Research Network. **Exploratory analysis of diabetic retinopathy progression through 3 years in a randomized clinical trial that compares intravitreal triamcinolone acetonide with focal/grid photocoagulation.** Arch Ophthalmol. 2009 Dec;127(12):1566-71 (Published).

6. Aiello LP, Edwards AR, Beck RW, Bressler NM, Davis MD, Ferris FL, Glassman AR, Ip MS, Miller KM, for the Diabetic Retinopathy Clinical Research Network. **Factors associated with improvement and worsening of visual acuity 2 years after focal/grid photocoagulation for diabetic macular edema.** Ophthalmology 2010 May;117(5):946-953 (Published).

7. Lauer AK, Bressler NM, Edwards AR, for the Diabetic Retinopathy Clinical Research Network. **Frequency of Intraocular Pressure Increase within Days After Intravitreal Triamcinolone Injections in the Diabetic Retinopathy Clinical Research Network.** Arch Ophthalmol. 2011 Aug;129(8):1097-1099. (Published).

Protocol C - OCT Diurnal Variation Study:

1. Diabetic Retinopathy Clinical Research Network, Danis RP, Glassman AR, Aiello LP, Antoszyk AN, Beck RW, Browning DJ, Ciardella AP, Kinyoun JL, Murtha TJ, Topping TM, Shami M, Sharuk GS, Wells JA 3rd. **Diurnal variation in retinal thickening measurement by optical coherence tomography in center-involved diabetic macular edema.** Arch Ophthalmol.2006 Dec;124(12):1701-7 (Published).

2. Diabetic Retinopathy Clinical Research Network, Krzystolik MG, Strauber SF, Aiello LP, Beck RW, Berger BB, Bressler NM, Browning DJ, Chambers RB, Danis RP, Davis MD, Glassman AR, Gonzalez VH, Greenberg PB, Gross JG, Kim JE, Kollman C. **Reproducibility of macular thickness and volume using Zeiss optical coherence tomography in patients with diabetic macular edema.** Ophthalmology.2007 Aug;114(8):1520-5 (Published).

Protocol D - Vitrectomy Study:

1. Diabetic Retinopathy Clinical Research Network Writing Committee on behalf of the DRCR.net, Haller JA, Qin H, Apte RS, Beck RW, Bressler NM, Browning DJ, Danis RP, Glassman AR, Googe JM, Kollman C, Lauer AK, Peters MA, Stockman ME. **Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction.** Ophthalmology. 2010 Jun;117:1087-1093.e3 (Published).

2. Diabetic Retinopathy Clinical Research Network. **Factors associated with visual acuity outcomes after vitrectomy for diabetic macular edema.** Retina. 2010 Oct;30(9):1488-95 (Published).

Protocol E - Peribulbar Triamcinolone Acetonide Study:

1. Diabetic Retinopathy Clinical Research Network, Chew E, Strauber S, Beck R, Aiello LP, Antoszyk A, Bressler N, Browning D, Danis R, Fan J, Flaxel C, Friedman S, Glassman A, Kollman C, Lazarus H.. **Randomized trial of peribulbar triamcinolone acetonide with and without focal photocoagulation for mild diabetic macular edema: a pilot study.** Ophthalmology.2007 Jun;114(6):1190-6 (Published).

2. Chew EY, Glassman AR, Beck RW, Bressler NM, Fish GE, Ferris FL, Kinyoun JL; Diabetic Retinopathy Clinical Research Network. **Ocular side effects associated with peribulbar injections of triamcinolone acetonide for diabetic macular edema.** Retina. 2011 Feb;31(2):284-9 (Published).

Protocol F - PRP Study:

1. Diabetic Retinopathy Clinical Research Network, Brucker AJ, Qin H, Antoszyk AN, Beck RW, Bressler NM, Browning DJ, Elman MJ, Glassman AR, Gross JG, Kollman C, Wells JA 3rd. **Observational study of the development of diabetic macular edema following panretinal (scatter) photocoagulation given in 1 or 4 sittings.** Arch Ophthalmol.2009 Feb;127(2):132-40 (Published).

Protocol G - Subclinical Diabetic Macular Edema Study:

1. Bressler NM, Edwards AR, Antoszyk AN, Beck RW, Browning DJ, Ciardella AP, Danis RP, Elman MJ, Friedman SM, Glassman AR, Gross JG, Li HK, Murtha TJ, Stone TW, Sun JK; Diabetic Retinopathy Clinical Research Network. **Retinal thickness on Stratus optical coherence tomography in people with diabetes and minimal or no diabetic retinopathy.** Am J Ophthalmol.2008 May;145(5):894-901 (Published).

2. Diabetic Retinopathy Clinical Research Network. **Observational Study of Subclinical Diabetic Macular Edema.** Eye (Lond). 2012 Jun;26(6):900-1 (Published).

Protocol H - Bevacizumab (Avastin) Phase 2 Study:

1. Diabetic Retinopathy Clinical Research Network, Scott IU, Edwards AR, Beck RW, Bressler NM, Chan CK, Elman MJ, Friedman SM, Greven CM, Maturi RK, Pieramici DJ, Shami M, Singerman LJ, Stockdale CR. **A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema.** Ophthalmology.2007 Oct;114(10):1860-7 (Published).

2. Scott IU, Bressler NM, Bressler SB, Browning DJ, Chan CK, Danis RP, Davis MD, Kollman C, Qin H; Diabetic Retinopathy Clinical Research Network Study Group. **Agreement between clinician and reading center gradings of diabetic retinopathy severity level at baseline in a phase 2 study of intravitreal bevacizumab for diabetic macular edema.** Retina.2008 Jan;28(1):36-40 (Published).

Protocol I - Laser-Ranibizumab-Triamcinolone for DME

1. Diabetic Retinopathy Clinical Research Network. **Expanded 2-year Follow-up of Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema.** Ophthalmology. 2011 Apr;118(4):609-14. (Published).

2. The Diabetic Retinopathy Clinical Research Network. **Rationale for the Diabetic Retinopathy Clinical Research Network Intravitreal Anti-VEGF Treatment and Follow-up Protocol for Center-involved Diabetic Macular Edema.** Ophthalmology. 2011 Dec;118:e5-e14 (Published).

3. Glassman AR, Stockdale CR, Beck RW, Baker C, Bressler NM; for the Diabetic Retinopathy Clinical Research Network. **Evaluation of Masking Study Participants to Intravitreal Injections in a Randomized Clinical Trial.** Arch Ophthalmol. 2012 Feb;130(2):190-194 (Published).

4. 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 June;117(6):1064-1077.e35 (Published).

5. Bressler S, Qin H, Beck RW, Chalam KV, Kim JE, Melia M, Wells JA, for the Diabetic Retinopathy Clinical Research Network. **Factors Associated with Changes in Visual Acuity and OCT Thickness at 1 Year after Treatment for Diabetic Macular Edema with Ranibizumab.** Arch Ophthalmol. 2012 Sep;130(9):1153-1161 (Published).

6. The Diabetic Retinopathy Clinical Research Network, Elman MJ, Qin H, Aiello LP, Beck RW, Bressler NM, Ferris FL III, Glassman AR, Maturi RK, Melia M. **Intravitreal Ranibizumab for Diabetic Macular Edema with Prompt vs Deferred Laser Treatment: 3-year Randomized Trial Results.** Ophthalmology 2012;119:2312–18 (Published).

7.Bressler SB, Qin H, Melia M, Bressler NM, Beck RW, Chan CK, Grover S, Miller DG, Stone T, for the Diabetic Retinopathy Clinical Research Network. **Exploratory Analysis of Effect of Intravitreal Ranibizumab or Triamcinolone on Worsening of Diabetic Retinopathy in a Randomized Clinical Trial.** JAMA Ophthalmol. 2013; 131(8):1033-1040 (Published).

8.Bressler SB, Almukhtar T, Aiello LP, Bressler NM, Ferris FL III, Glassman AR, Greven CM, for the Diabetic Retinopathy Clinical Research Network. **Green or Yellow Laser Treatment for Diabetic Macular Edema: Exploratory Assessment within the Diabetic Retinopathy Clinical Research Network.** Retina. 2013 Nov- Dec;33(10):2080-8. (Published).

9. Bressler SB, Almukhtar T, Bhorade A, Bressler NM, Glassman AR, Huang S, Jampol LM, Kim JE, Melia M, for the Diabetic Retinopathy Clinical Research Network. **Repeated Intravitreous Ranibizumab Injections for Diabetic Macular Edema and the Risk of Sustained IOP Elevation or Ocular Hypotensive Treatment.** JAMA Ophthalmol. JAMA Ophthalmol. 2015 May 1;133(5):589-97. (Published).

10. Bressler SB, Melia M, Glassman AR, Almukhtar T, Jampol LM, Shami M, Berger BB, Bressler NM, for the Diabetic Retinopathy Clinical Research Network. **Ranibizumab plus prompt or deferred laser for diabetic macular edema in eyes with vitrectomy prior to anti-vascular endothelial growth factor therapy.** Retina. 2014 (Accepted).

11. Elman MJ, Ayala A, Bressler NM, Browning D, Flaxel CJ, Glassman AR, Jampol LM, Stone TW; Diabetic Retinopathy Clinical Research Network. **Intravitreal Ranibizumab for Diabetic Macular Edema with Prompt versus Deferred Laser Treatment: 5-Year Randomized Trial Results.** Ophthalmology. 2015 Feb;122(2):375-81. (Published).

Protocol J - Laser-Ranibizumab-Triamcinolone for DME Plus PRP

1. 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 June;31 (6):1009-27 (Published).

Protocol K - Laser Response

1. Diabetic Retinopathy Clinical Research Network. **The course of response to focal/grid photocoagulation for diabetic macular edema.** Retina.2009 Nov-Dec;29(10):1436-43 (Published).

Protocol L - Autorefraction and VA Reproducibility Study

1. The Diabetic Retinopathy Clinical Research Network. **Evaluation of Visual Acuity Measurements after Autorefraction versus Manual Refraction in Eyes with and without Diabetic Macular Edema.** Arch Ophthalmol. 2012 Apr; 130:470-479 (Published).

Protocol N - Intravitreal Ranibizumab for Vitreous Hemorrhage from PDR Study

1. Diabetic Retinopathy Clinical Research Network. **Randomized Clinical Trial Evaluating Intravitreal Ranibizumab or Saline for Vitreous Hemorrhage from Proliferative Diabetic Retinopathy.** JAMA Ophthalmol. 2013 Mar 1;131(3):283-93. doi: 10.1001/jamaophthalmol.2013.2015. (Published).

2. Bhavsar AR, Torres K, Bressler NM, Glassman AR, Jampol LM, Kinyoun JL, for the Diabetic Retinopathy Clinical Research Network. **One Year Results Evaluation Following Short Term Use of Ranibizumab for Vitreous Hemorrhage Due to Proliferative Diabetic Retinopathy.** JAMA Ophthalmol. July 2014;132(7):889- 890 (Published).

Protocol O - TD/SD OCT Comparison and Reproducibility

1. Diabetic Retinopathy Clinical Research Network. **Retinal Thickness in People with Diabetes and Minimal or No Diabetic Retinopathy: Heidelberg Spectralis Optical Coherence Tomography.** IOVS December 2012 53:8154-8161 (Published).

2.Diabetic Retinopathy Clinical Research Network. **Reproducibility of Optovue RTVue Optical Coherence Tomography Retinal Thickness Measurements and Conversion to Equivalent Zeiss Stratus Metrics in Diabetic Macular Edema.** JAMA Ophthal. 2014 *(Submitted for Publication)*.

3.Diabetic Retinopathy Clinical Research Network Writing Committee. **Reproducibility of spectral-domain optical coherence tomography retinal thickness measurements and conversion to equivalent time- domain metrics in diabetic macular edema.** JAMA Ophthalmol. Published online July 24, 2014. doi:10.1001/jamaophthalmol.2014.1698 (Published).

Protocol P - Cataract Surgery with Center-Involved DME Study

1. Diabetic Retinopathy Clinical Research Network. **Pilot Study of Individuals with Diabetic Macular Edema Undergoing Cataract Surgery.** JAMA Ophthalmol. 2014 Feb 1;132(2):224-6. (Published).

Protocol Q - Cataract Surgery without Center-Involved DME Study

1. Diabetic Retinopathy Clinical Research Network. Writing Committee: Baker CW, Almukhtar T, Bressler NM, Glassman AR, Grover S, Kim SJ, Murtha TJ, Rauser ME, Stockdale C.. **Macular Edema After Cataract Surgery In Eyes Without Pre-operative Central-involved Diabetic Macular Edema.** JAMA Ophthalmol. 2013 Jul;131 (7):870-9. (Published).

Protocol R - Phase II non-Central DME NSAID Study

1.Friedman SM, Almukhtar TH, Baker CW, Glassman AR, Elman MJ, Bressler NM, Maker MP, Jampol LM, Melia M, Diabetic Retinopathy Clinical Research Network. **Topical Nepafenec in Eyes with Non-Central Diabetic Macular Edema.** Retina. 2015 May;35(5):944-56.

Protocol S - Prompt PRP vs Ranibizumab+Deferred PRP for PDR Study

1. Diabetic Retinopathy Clinical Research Network. Panretinal Photocoagulation vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Trial. JAMA. Published online November 13, 2015. doi:10.1001/jama.2015.15217 (In-Press).
2. Gross JG, Glassman AR, Liu D, Sun JK, Antoszyk AN, Baker CW, Bressler NM, Elman MJ, Ferris FL 3rd, Gardner TW, Jampol LM, Martin DF, Melia M, Stockdale CR, Beck RW; Diabetic Retinopathy Clinical Research Network. Five-Year Outcomes of Panretinal Photocoagulation vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. JAMA Ophthalmol. 2018 Jul 24. doi: 10.1001/jamaophthalmol.2018.3255. [Epub ahead of print] PubMed PMID: 30043039.

Protocol T - Aflibercept, Bevacizumab and Ranibizumab Comparison for DME Study

1. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, Antoszyk AN, Arnold-Bush B, Baker CW, Bressler NM, Browning DJ, Elman MJ, Ferris FL, Friedman SM, Melia M, Pieramici DJ, Sun JK, Beck RW. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015 Mar 26;372(13):1193-203. PubMed PMID: 25692915; PubMed Central PMCID: PMC4422053.
2. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, Brucker AJ, Ferris FL, Hampton GR, Jhaveri C, Melia M, Beck RW; Diabetic Retinopathy Clinical Research Network. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. Ophthalmology. 2016 Jun;123(6):1351-9. PMID: 26935357

Protocol U - Dexamethasone for Patients With Persistent Diabetic Macular Edema

Maturi RK, Glassman AR, Liu D, Beck RW, Bhavsar AR, Bressler NM, Jampol LM, Melia M, Punjabi OS, Salehi-Had H, Sun JK; Diabetic Retinopathy Clinical Research Network. Effect of Adding Dexamethasone to Continued Ranibizumab Treatment in Patients With Persistent Diabetic Macular Edema: A DRCR Network Phase 2 Randomized Clinical Trial. JAMA Ophthalmol. 2018 Jan 1;136(1):29-38. PMID: 29127949

CLARITY Trial –

Sivaprasad S, Prevost AT, Vasconcelos JC, Riddell A, Murphy C, Kelly J, Bainbridge J, Tudor-Edwards R, Hopkins D, Hykin P; CLARITY Study Group. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicenter, single-blinded, randomized, controlled, phase 2b, non-inferiority trial. Lancet. 2017 Jun 3;389(10085):2193-2203. PubMed PMID: 28494920.