Clinical Trials in Diabetic Retinopathy

2018

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(8) READ-2 Study

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

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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

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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

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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

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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 © 2015 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

(9) Results from RIDE and RISE

Vision-Related Function after Ranibizumab Treatment for Diabetic Macular Edema

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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 86 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

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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

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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

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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

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Protocol Q - Cataract Surgery without Center-Involved DME Study

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Protocol R - Phase II non-Central DME NSAID Study

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

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

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