ONLINE FIRST

Long-term Effects of Ranibizumab on Diabetic Retinopathy Severity and Progression

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Objective: To evaluate effects of intravitreal ranibizumab on diabetic retinopathy (DR) severity over time in 2 phase 3 clinical trials (RIDE, NCT00473382; RISE, NCT00473330) of ranibizumab for diabetic macular edema.

Methods: Participants with diabetic macular edema (n=759) were randomized to monthly sham, 0.3-mg ranibizumab, or 0.5-mg ranibizumab intravitreal injections. Macular laser was available per protocol-specified criteria. Fundus photographs, taken at baseline and periodically, were graded by a central reading center; clinical examinations were performed monthly. The main outcome measures of this report are secondary/exploratory analyses including a 2-step or more and 3-step or more change on the Early Treatment Diabetic Retinopathy Study severity scale in the study eye and a composite DR progression outcome including photographic changes plus clinically important events such as occurrence of vitreous hemorrhage or need for panretinal laser.

Results: At 2 years, the percentage of participants with DR progression (worsening by ≥2 or ≥3 steps) was significantly reduced in ranibizumab-treated eyes compared with sham-treated eyes, and DR regression (improving by ≥2 or ≥3 steps) was significantly more likely. The cumulative probability of clinical progression of DR as measured by the composite outcome at 2 years was 33.8% of sham-treated eyes compared with 11.2% to 11.5% of ranibizumab-treated eyes.

Conclusions: Intravitreal ranibizumab reduced the risk of DR progression in eyes with diabetic macular edema, and many ranibizumab-treated eyes experienced improvement in DR severity. Because these results are exploratory, the use of intravitreal ranibizumab specifically to reduce DR progression or cause DR regression requires further study.

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DIABETIC RETINOPATHY (DR), a common microvascular complication of diabetes mellitus, is defined by characteristic lesions ranging from retinal microaneurysms to neovascularization.[1] Two general DR subtypes exist: nonproliferative (NPDR) and proliferative (neovascular) (PDR); diabetic macular edema (DME) is a complication that may coexist with both.[2,3] Diabetic retinopathy progresses (worsens) in discrete steps, which are defined in the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale.[4] With each advancing level of severity, the risk of developing DME and/or complications of PDR increases; both 2-step or more and 3-step or more worsening on the ETDRS severity scale are associated with an increased risk of subsequent vision loss over time.[5] Proliferative DR may be accompanied by complications such as vitreous hemorrhage, traction retinal detachment, and neovascular glaucoma, resulting in substantial and potentially irreversible visual loss and the need for medical or surgical interventions that carry substantial morbidity.[1] In the United States, diabetes is the leading cause of new cases of blindness in working-aged adults, and both DME and PDR are significant and growing public health problems.[6]

Current treatment for PDR, once clinically defined threshold criteria are met, is panretinal photocoagulation (PRP), which has been shown to reduce the rate of severe vision loss by 50%.[1,7] Although PRP is generally well tolerated, potential adverse effects may include peripheral visual field loss, dyschromatopsia, nyctalopia, and reduced central acuity from exacerbation of concomitant DME; however, the long-term benefits clearly outweigh the risks.[1,8] Nevertheless, it would be desirable to both have less tissue-destructive treatments for PDR and novel approaches for reducing the risk of its development.

At present, several well-recognized approaches reduce the rate of progression of NPDR to PDR. One is the early application of PRP in eyes with advanced NPDR, as demonstrated in the ETDRS.[8] How-

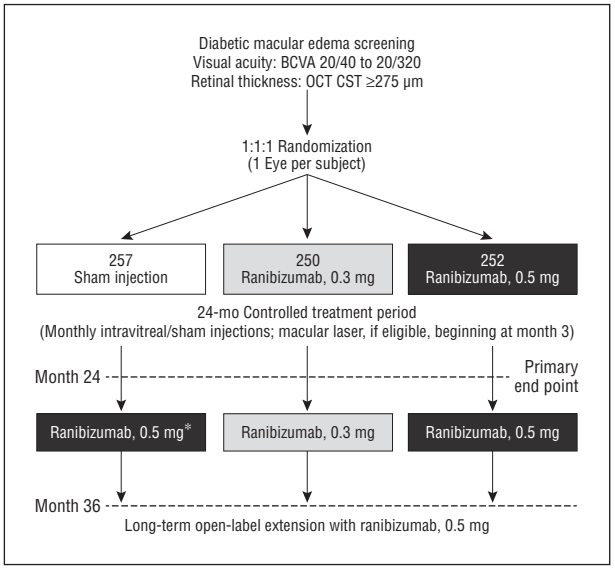

Figure 1. RIDE and RISE clinical trial design. BCVA indicates best-corrected visual acuity; CST, central subfield thickness; and OCT, optical coherence tomography. *Participants in the sham arm were allowed to cross over to monthly treatment with 0.5 mg of ranibizumab in their third year of study participation.

ever, because PRP is destructive, it is typically used judiciously to treat eyes with advanced NPDR. From a systemic perspective, improvements in management of hyperglycemia, hypertension, and hyperlipidemia all have shown potential benefits of reduced DR progression.[9-12]

The actual regression (improvement) of NPDR from more advanced levels to less severe levels of NPDR would be desirable, since regression would presumably reduce the risk of subsequent vision loss. Trends toward regression of NPDR were demonstrated in several clinical trials. Treatment with candesartan cilexetil resulted in both reduction in DR progression and improvements in retinopathy severity.[12] However, the results did not meet statistical significance, and candesartan is not commonly used as a primary DR therapy. Regression of DR has also been demonstrated in studies of intravitreal corticosteroids for DME. Despite these observations, corticosteroids are not used for inducing retinopathy regression or preventing retinopathy progression because of the risks of glaucoma and cataract.[13-15]

Preclinical and clinical data suggest that the pathophysiology of both NPDR and PDR are mediated, at least in part, by vascular endothelial growth factor (VEGF).[16-19] Thus, inhibition of intraocular VEGF may slow retinopathy progression and potentially also cause DR regression. This hypothesis is supported indirectly by the beneficial effects on retinopathy described earlier for corticosteroids, which may mediate intraocular VEGF expression,[20,21] and more directly from the results of several phase 3 clinical trials in DME examining the effects of ranibizumab, an anti-VEGF monoclonal antibody fragment designed for intraocular use.[14,22]

Diabetic retinopathy progression can be evaluated by the standardized ETDRS severity scale (using fundus photographs) and by several important clinical outcomes such as occurrence of vitreous hemorrhage, need for vitrectomy, and use of panretinal laser. The present exploratory analysis comprehensively evaluates changes in DR severity in participants with DME following 2 years of monthly exposure to ranibizumab.

METHODS

CLINICAL TRIAL DESIGN

RIDE (NCT00473382) and RISE (NCT00473330) are methodologically identical, phase 3, double-masked, sham injection–controlled randomized clinical trials of ranibizumab in DME (**Figure 1**).[22] Study protocols were approved by institutional review boards and ethics committees. Participants provided written informed consent. Details of the methods and key visual acuity and safety findings have been described.[22] Aspects of the study designs relevant to these analyses are described herein.

Individuals 18 years and older with decreased vision due to DME (study eye best-corrected visual acuity of 20/40 to 20/320 approximate Snellen equivalent) and central subfield thickness of 275 µm or more were eligible for enrollment. Ocular exclusion criteria included a recent history (within 3 months of screening) of PRP, macular laser photocoagulation, or intraocular corticosteroids, history of vitreoretinal surgery in the study eye, and use of antiangiogenic drugs in either eye within 3 months of day 0. Participants with active PDR or uncontrolled glaucoma in the study eye were excluded. One eye per patient was randomized to monthly sham injections or intravitreal injections of 0.3 mg or 0.5 mg of ranibizumab through month 24 (Figure 1). Macular laser was available per protocol-specified criteria, beginning at month 3.[22]

GRADING PROTOCOL

Stereoscopic 7-field color fundus photographs were obtained at each subject's screening visit and at months 3, 6, 12, 18, and 24. Photographs were evaluated at the University of Wisconsin Fundus Photograph Reading Center by trained evaluators masked to both treatment assignment and images from previous visits. Each eye was graded by 2 evaluators. In case of disagreement in severity level by more than 1 step, grades were adjudicated by a third senior grader. Retinopathy severity was graded according to a 9-step ETDRS severity scale using summary grading, in which the evaluator reviewed all fields and then assigned the grade based on the most severe lesion(s) seen in the eye.[4] The ETDRS severity scale for individual eyes was used, as follows: DR absent (levels 10 and 12); DR questionable, microaneurysms only (levels 14, 15, and 20); mild NPDR (level 35); moderate NPDR (level 43); moderately severe NPDR (level 47); severe NPDR (level 53); prior scars of PRP or mild PDR (levels 60 and 61); moderate PDR (level 65); and high-risk PDR (levels 71, 75, 81, and 85). Participants with a history of PRP (24% of those randomized) were assigned to a minimum severity level of 60. These participants may worsen in retinopathy severity but cannot improve to a score less than 60 by definition.

CLINICAL ASSESSMENTS OF DR PROGRESSION OVER TIME

Based on modification of a hierarchical DR progression algorithm proposed by Bressler et al,[13] we defined clinically important progression as including any of the following: progression from NPDR (ETDRS DR severity level <60) to PDR (ETDRS DR severity level ≥ 60) on fundus photographs; use of panretinal laser; occurrence of vitreous hemorrhage; identification by ophthalmoscopy; performance of vitrectomy for PDR-related reasons; and occurrence of iris or retinal neovascularization adverse events. Subjects with DR progression defined by more than 1 event were counted only once.

Table 1. Baseline Fundus Photograph Characteristics of the Study Eye

Characteristic	Pooled Randomized Participants (RIDE and RISE), No. (%)[a]		
		Ranibizumab	
	Sham (n = 254)	0.3 mg (n = 245)	0.5 mg (n = 247)
ETDRS DR severity level			
1 = DR severity levels 10 and 12 (DR absent)	1 (0.4)	1 (0.4)	1 (0.4)
2 = DR severity levels 14A-14C, 14Z, 15, and 20 (DR questionable, microaneurysms only)	3 (1.2)	3 (1.2)	3 (1.2)
3 = DR severity levels 35A-35F (mild NPDR)	38 (15.0)	39 (15.9)	42 (17.0)
4 = DR severity levels 43A-43B (moderate NPDR)	33 (13.0)	29 (11.8)	34 (13.8)
5 = DR severity levels 47A-47D (moderately severe NPDR)	72 (28.3)	74 (30.2)	64 (25.9)
6 = DR severity levels 53A-53E (severe NPDR)	14 (5.5)	14 (5.7)	10 (4.0)
7 = DR severity levels 60, 61A, and 61B (mild PDR)	64 (25.2)	64 (26.1)	69 (27.9)
8 = DR severity levels 65A-65C (moderate PDR)	12 (4.7)	7 (2.9)	9 (3.6)
9 = DR severity levels 71A-71D (high-risk PDR)	2 (0.8)	3 (1.2)	1 (0.4)
10 = DR severity level 75 (high-risk PDR)	0	0	1 (0.4)
90 = DR severity level 90 (cannot grade)	15 (5.9)	11 (4.5)	13 (5.3)
Focal and/or grid photocoagulation for macular edema			
None	35 (13.8)	28 (11.4)	21 (8.5)
Questionable	53 (20.9)	40 (16.3)	49 (19.8)
Definite	162 (63.8)	172 (70.2)	174 (70.4)
Cannot grade	4 (1.6)	5 (2.0)	3 (1.2)
Panretinal photocoagulation			
None	169 (66.5)	165 (67.3)	161 (65.2)
Questionable	10 (3.9)	13 (5.3)	8 (3.2)
Partial scatter or local photocoagulation for NV	7 (2.8)	6 (2.4)	7 (2.8)
Complete scatter (± local)	58 (22.8)	60 (24.5)	62 (25.1)
Cannot grade	10 (3.9)	1 (0.4)	9 (3.6)
Retinal thickening at center of macula			
None	0	1 (0.4)	0
Questionable	0	1 (0.4)	1 (0.4)
Definite, <1× reference	9 (3.5)	5 (2.0)	10 (4.0)
Definite, <2× reference	144 (56.7)	144 (58.8)	137 (55.5)
Definite, ≥2× reference	91 (35.8)	77 (31.4)	87 (35.2)
Cannot grade	10 (3.9)	17 (6.9)	12 (4.9)

Abbreviations: DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; NPDR, nonproliferative DR; NV, new vessels; PC, photocoagulation; PDR, proliferative DR.
[a] Randomized participants with baseline fundus photograph characteristics of the study eye.

STATISTICAL ANALYSES

Since the baseline distributions of retinopathy severity were similar across both studies, data were pooled for these analyses. Study eye ETDRS severity level was summarized over time. The number of study eyes progressing (worsening) or regressing (improving) 2 or more or 3 or more steps from baseline were summarized at month 12 or month 24 for all study eyes and by baseline study eye ETDRS DR severity level (53E or less severe vs 60 or more severe). Cochran-Mantel-Haenszel χ^2 tests stratified for baseline study eye visual acuity letter score (≤55 vs >55), baseline hemoglobin A_{1c} level (≤8% vs >8%), and prior treatment for DME in the study eye (yes vs no) were used to compare the progression and regression rates between the ranibizumab groups vs the sham group. The number of fellow (nonstudy) eyes progressing or regressing 2 or more steps or 3 or more steps from baseline overall were summarized; Pearson χ^2 tests were used to compare these results between the ranibizumab groups vs the sham group. The last observation carried forward method was used to impute missing data.

Time to first DR progression was analyzed using Kaplan-Meier methods to calculate cumulative probabilities by treatment group. The Cox proportional hazard model stratified by baseline study eye visual acuity letter score (≤55 vs >55), baseline hemoglobin A_{1c} level (≤8% vs >8%), prior treatment for DME in the study eye (yes vs no), and baseline study eye ETDRS DR severity level (53E or less severe vs 60 or more severe) was used to compare the risk of DR progression in the ranibizumab groups vs the sham group.

RESULTS

Seven hundred fifty-nine participants with DME were randomized to sham or ranibizumab (Figure 1); baseline fundus photograph characteristics of the study eye, which were well balanced across groups, were available for 746 (**Table 1**; eTable, http://www.archophthalmol.com).

CHANGES IN PHOTOGRAPHICALLY DETERMINED DR SEVERITY OVER TIME

The distribution of and median DR severity levels at baseline and over time for each treatment group are summarized in **Figure 2**. In the sham group, the median DR severity level remained at moderately severe NPDR through 24 months. In the ranibizumab groups, the median DR severity level improved over time, from mod-

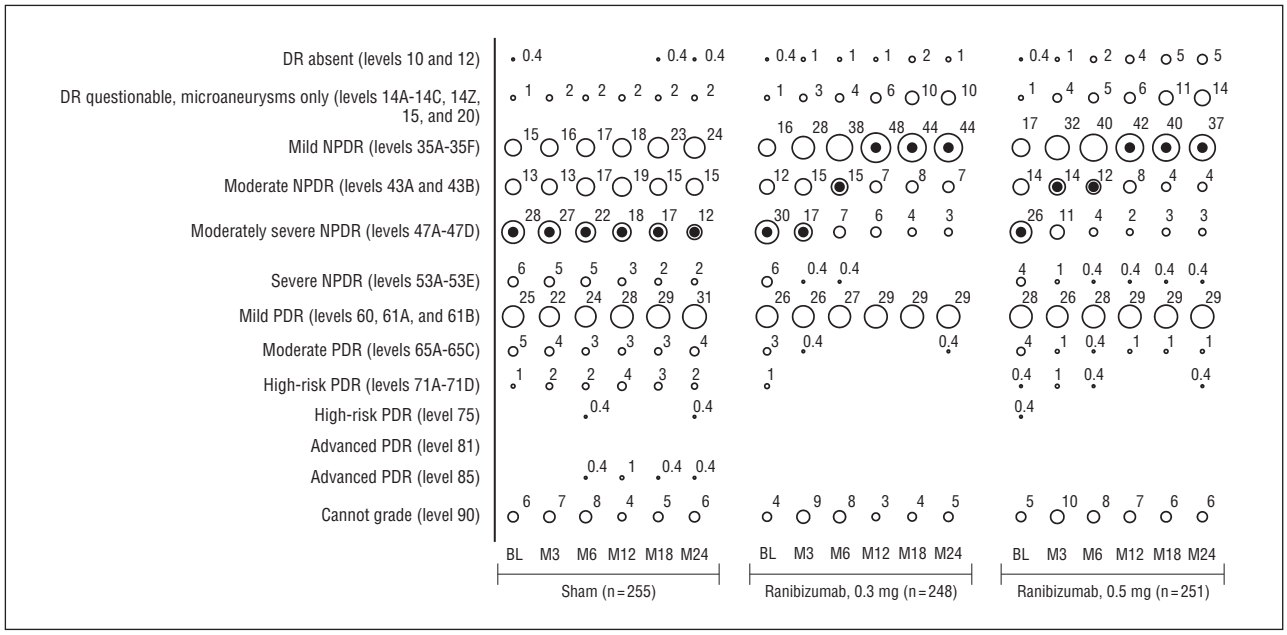

Figure 2. Distribution of Early Treatment Diabetic Retinopathy Study (ETDRS) diabetic retinopathy (DR) severity levels over time. Reported values are the percentage of participants with the stated level of DR severity at each visit per treatment group. Percentages in each time column add up to 100%. Bubble sizes are proportional to the percentage of participants in each ETDRS DR severity level grouping in a column. The solid black dot indicates the median DR severity level in each column. Sham/0.3 mg of ranibizumab/0.5 mg of ranibizumab: baseline (BL), n=254/245/247; month 3 (M3), n=255/246/249; and month 6 (M6), n=255/246/250. M12 indicates month 12; M18, month 18; M24, month 24; NPDR, nonproliferative DR; and PDR, proliferative DR.

erately severe NPDR at baseline to mild NPDR at month 24. The proportion of participants with mild NPDR (levels 35A-35F) increased from 16% and 17% at baseline to 44% and 37% at month 24 in the 0.3-mg and 0.5-mg ranibizumab groups, respectively, compared with a change from 15% to 24% in the sham group. This was paralleled by corresponding substantial decreases in the proportions of participants with moderate, moderately severe, and severe NPDR in the ranibizumab groups. Additionally, although relatively few participants in all groups developed advanced PDR, the proportion was smaller in the ranibizumab groups. Because participants with a history of PRP have a minimum score of 60 (mild PDR or scars of prior PRP) by definition, the proportion of participants with "mild PDR" remained relatively unchanged across all groups.

CHANGE FROM BASELINE ETDRS DR SEVERITY LEVEL AT MONTH 24

Significantly fewer eyes treated with ranibizumab worsened (progressed) by 2 or more or 3 or more steps on the ETDRS severity scale from baseline to month 24 compared with the sham group (**Figure 3**; for month 12 data, see eFigure 1). Furthermore, study eyes receiving ranibizumab were significantly more likely to improve by 2 or more or 3 or more steps on the ETDRS severity scale from baseline to month 24 compared with the sham group (Figure 3; for month 12 data, see eFigure 1). To control for patient-level changes that could possibly affect both study and fellow eyes, we examined the distribution of 2-step or more or 3-step or more changes in fellow (nonstudy) eyes as well; no statistically significant differences were observed in fellow eyes of participants whose study eyes were randomized to sham vs ranibizumab (Figure 3; for month 12 data, see eFigure 1). **Figure 4** provides examples of DR regression (improvements in microaneurysms, intraretinal hemorrhages, and retinal neovascularization) in study participants treated with ranibizumab.

RESPONSE TO TREATMENT STRATIFIED BY STUDY EYE ETDRS DR SEVERITY LEVEL AT BASELINE

Because baseline retinopathy status may affect both the rate and extent of subsequent DR severity changes over time and because participants with a history of PRP cannot improve to an ETDRS severity level better than 60, we performed a subgroup analysis stratifying the population by baseline DR severity (**Figure 5**; for month 12 data, see eFigure 2). Results were similar to those in the overall population. Ranibizumab-treated eyes were more likely to experience improvements in retinopathy severity and less likely to experience worsening. Notably, among study eyes with baseline ETDRS severity level of 53E (severe NPDR) or less, the proportion of participants with 2 or more steps of improvement at month 24 in the sham, 0.3-mg ranibizumab, and 0.5-mg ranibizumab groups was 6.8%, 46.9%, and 46.8%, respectively ($P < .001$ for each comparison of ranibizumab vs sham).

CLINICAL ASSESSMENTS OF DR PROGRESSION OVER TIME

Although changes on the ETDRS severity scale are an objective, independent way to evaluate DR severity over time, limiting analysis to the photographic scale necessitates that additional markers of DR progression be ignored or discarded. Additionally, because color fundus photo-

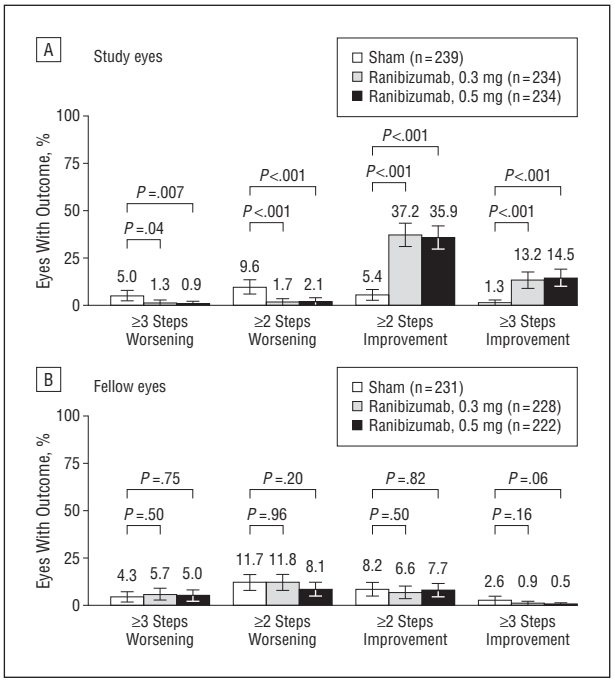

Figure 3. Change from baseline in Early Treatment Diabetic Retinopathy Study diabetic retinopathy severity level at month 24 in study eyes (A) and fellow eyes (B). Vertical bars are 95% confidence intervals (unadjusted).

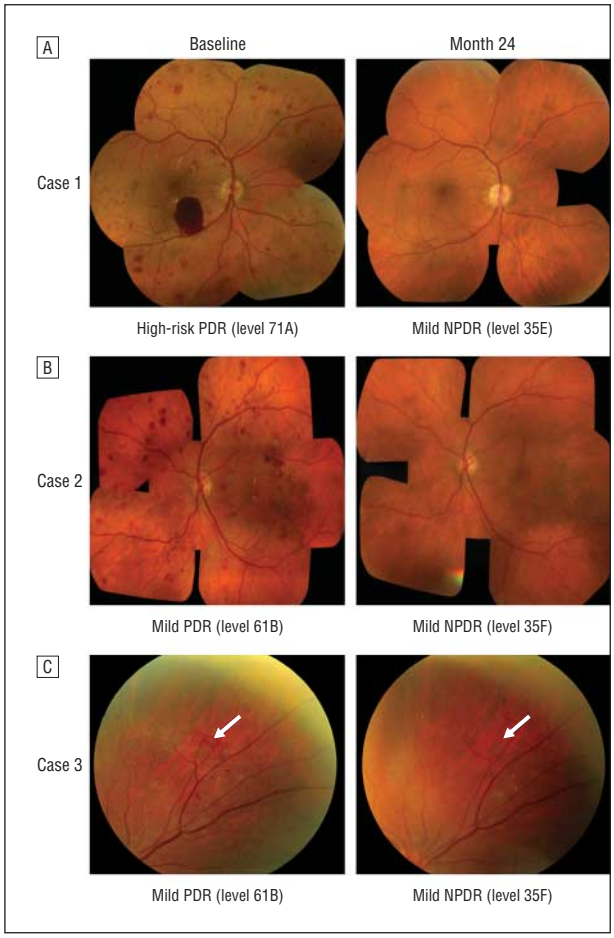

Figure 4. Baseline and month 24 fundus photographs from 3 participants randomized to ranibizumab showing substantial regression of retinopathy level (A-C). In case 3 (C), the arrow indicates an area of neovascularization at baseline and the same area showing absence of neovascularization at month 24. NPDR indicates nonproliferative diabetic retinopathy; and PDR, proliferative diabetic retinopathy.

graphs were taken periodically, clinically important DR progression events occurring between photographic assessments may have been missed. Thus, based on modification of a hierarchical DR progression algorithm proposed by Bressler et al,[13] we also analyzed DR progression using a composite outcome incorporating this additional clinical information (**Table 2**). Time to first DR progression from baseline using this composite analysis demonstrates that the rate of DR progression was significantly reduced by treatment with ranibizumab. A total of 30 sham-treated patients underwent PRP over 2 years, as compared with 2 and 3 patients in the 0.3-mg and 0.5-mg ranibizumab groups. Similarly, over 2 years, 42 sham-treated patients developed vitreous hemorrhage, compared with 13 and 11 in the 0.3-mg and 0.5-mg ranibizumab groups; 16 sham-treated patients underwent vitrectomy for DR-related reasons vs 0 and 3 patients in the 0.3-mg and 0.5-mg ranibizumab groups. By month 24, the cumulative probability of DR progression using the composite analysis was 33.8% of sham-treated participants and 11.2% to 11.5% of participants randomized to ranibizumab (**Figure 6**) ($P<.001$ for each comparison of ranibizumab vs sham).

COMMENT

These analyses demonstrate that intraocular VEGF inhibition with ranibizumab reduces the risk of DR progression and in many cases regresses DR pathology. The relative benefit of ranibizumab was similar whether DR progression was assessed using solely the ETDRS severity scale or a composite analysis including other markers of DR progression such as development of vitreous hemorrhage, application of panretinal laser, or vitrectomy. Very few participants with DME treated with ranibizumab experienced a 2-step or more progression of retinopathy severity after 2 years (1.7%-2.1% of ranibizumab-treated participants vs 9.6% of sham-treated participants) (Figure 3). The relative risk reduction is greater than that previously observed for other ocular or systemic DR interventions.[9] Additionally, at 2 years, more than one-third of ranibizumab-treated eyes experienced a 2-step or more regression of retinopathy severity with ranibizumab treatment compared with 5.4% of sham control eyes. These modest improvements seen in the sham group are most likely due to either improved diabetic control in some patients and/or natural fluctuations in DR severity. Theoretically, these improvements in the sham group may be due to use of macular laser (which was available to all patients per protocol-specified criteria and administered to 72% of sham-treated patients at least once),[22] but this is unlikely since macular laser does not appear to have an effect on retinopathy level.[13] Differences in DR severity between sham- and ranibizumab-treated eyes were seen early after initiation of treatment and persisted across the 2-year treatment period.

Reductions in DR progression were also demonstrated in several studies evaluating corticosteroids for

DME. Furthermore, poor clinical outcomes related to development of proliferative disease were reduced in eyes treated with triamcinolone.[13] Despite these beneficial effects on DR, triamcinolone conveys no long-term visual acuity advantage compared with macular laser for DME[14] and carries risks for the development of cataracts and glaucoma. Anti-VEGF therapy has also been previously seen to retard retinopathy progression and, in some cases, result in regression of retinopathy severity; our results are consistent with these previous observations both with ranibizumab and pegaptanib.[14,23] That VEGF inhibition alone can halt DR progression or reverse DR severity suggests that progression is significantly, if not primarily, VEGF mediated.

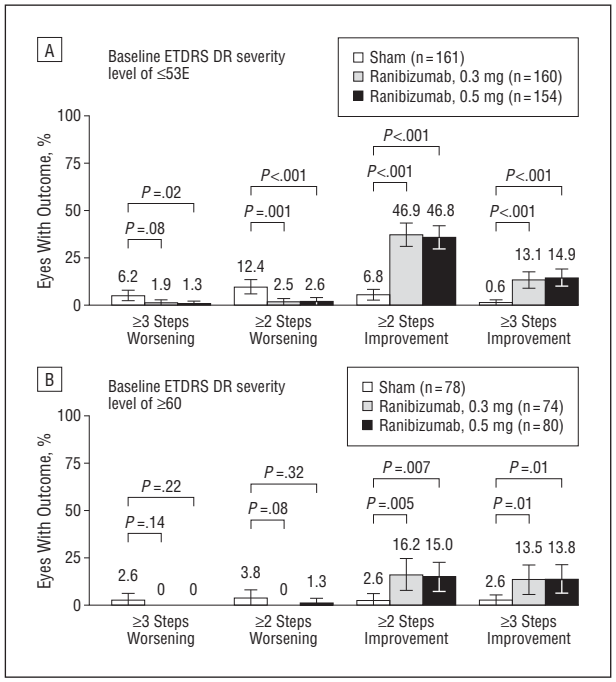

Figure 5. Study eye change from baseline in Early Treatment Diabetic Retinopathy Study (ETDRS) diabetic retinopathy (DR) severity level at month 24 by baseline study eye severity level (level ≤53E [A] and level ≥60 [B]). Vertical bars are 95% confidence intervals (unadjusted).

The major strengths of this report are that the clinical data (such as ocular examination findings and use of panretinal laser) were obtained from large multicenter randomized clinical trials and that fundus photographs were obtained frequently and evaluated by an independent reading center. Evaluators were masked to treatment assignment, and all photographs were evaluated according to a strict protocol. Moreover, unlike prior studies evaluating DR severity in eyes treated with corticosteroids, cataracts were no more likely to develop during the study period in ranibizumab-treated participants than in sham-treated participants.[22] The low rate of ungradable photographs due to cataracts makes it likely that retinopathy regression or progression was detected accurately and evenly across the sham and ranibizumab groups.

One limitation of our analysis is that the ETDRS DR severity changes were not the primary statistical outcome of the studies; rather, these were secondary and exploratory analyses of studies whose primary purpose was to evaluate the safety and efficacy of ranibizumab in DME. Despite this, the differences in proportions of ranibizumab- and sham-treated study eyes with progression or improvement in DR severity level were so large that they were unlikely to have occurred by chance. There are other more clinically relevant limitations. First, our studies enrolled only participants experiencing vision loss from DME; the results observed on DR progression and regression may not be applicable to the larger population of NPDR participants without DME. However, preclinical data and our clinical observations suggest that many aspects of DR pathophysiology, not just edema, are mediated by VEGF.[19] Second, ranibizumab was administered monthly, and results on DR progression might differ with less frequent treatment; however, changes in retinopathy progression were noted with less frequent dosing of ranibizumab in other clinical studies.[14] Finally, and perhaps most importantly, our studies did not

Table 2. Cumulative No. of DR Progression Cases During the 24-Month Controlled Treatment Period

	Cumulative No. of Participants With DR Progression					
	Baseline to Year 1			Baseline to Year 2		
		Ranibizumab			Ranibizumab	
Progression Category	Sham (n = 257)	0.3 mg (n = 250)	0.5 mg (n = 252)	Sham (n = 257)	0.3 mg (n = 250)	0.5 mg (n = 252)
Total cases that progressed from NPDR (DR severity level <60 at baseline) to PDR (level ≥60 later)[a]	10	2	0	21	5	5
Total/additional (not counted in row above) cases that received PRP laser	17/15	1/1	3/3	30/20	2/2	3/2
Total/additional (not counted in 2 rows above) cases that reported vitreous hemorrhage (AE or slitlamp grade 0 at baseline, grade >0 later)	26/17	7/7	3/3	42/25	13/13	11/9
Total/additional (not counted in 3 rows above) cases identified by ophthalmoscopy	18/4	1/0	8/7	34/10	6/4	12/9
Total/additional (not counted in 4 rows above) cases that received vitrectomy	6/2	0/0	2/1	16/2	0/0	3/0
Total/additional (not counted in 5 rows above) cases that reported iris neovascularization (AE)	0/0	0/0	0/0	2/0	1/0	1/0
Total/additional (not counted in 6 rows above) cases that reported retinal neovascularization (AE)	14/0	1/1	5/1	24/0	2/1	6/1
Progression of retinopathy (total of all rows above)	48	11	15	78	25	26

Abbreviations: AE, adverse event; DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation.
[a]Calculated on the basis of reading center assessment of fundus photographs.

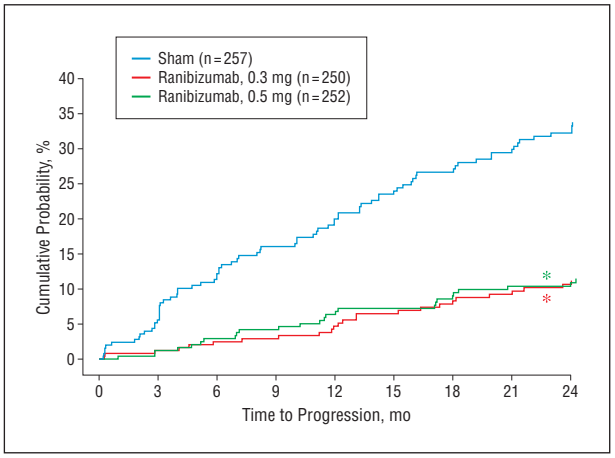

Figure 6. Time to first diabetic retinopathy (DR) progression from baseline in the pooled RIDE and RISE population. Cumulative probabilities were calculated using the Kaplan-Meier method. Progression was defined by (1) progression from nonproliferative diabetic retinopathy (DR severity level <60) at baseline to proliferative diabetic retinopathy (DR severity level ≥60) at a later time, (2) need for panretinal photocoagulation laser, (3) vitreous hemorrhage (adverse event [AE] or slitlamp grade 0 at baseline to >0 at a later time), (4) cases identified by ophthalmoscopy, (5) vitrectomy, (6) iris neovascularization AE event, or (7) retinal neovascularization AE. *P<.001 vs sham.

address subsequent changes in retinopathy severity if ranibizumab therapy was discontinued. Because the studies did not assess effects of ranibizumab withdrawal, it is unknown whether retinopathy severity will progress at the prior rate following cessation of therapy or whether there may be a rebound effect of rapid retinopathy progression. Additionally, it remains unanswered if restarting therapy after a prolonged interruption may once again have a beneficial effect on retinopathy severity. These questions would need to be answered in specifically designed clinical trials.

Ranibizumab has been found, in multiple clinical studies, to have beneficial effects on visual acuity in participants with DME, and anti-VEGF therapy is commonly and increasingly used as a primary treatment for DME.[14,22,24] At present, the main alternative to anti-VEGF therapy is macular laser. Our observations on DR progression and regression indicate that ranibizumab has potential benefits on DR severity, aside from improved visual acuity outcomes, and this may support the use of ranibizumab over macular laser (or in combination with laser) in eyes where either therapy may be contemplated. The current analysis does not yet support the use of ranibizumab primarily for control or regression of DR severity. The cumulative risks of intravitreal injections may outweigh the benefit of preventing DR progression or causing DR regression, particularly in participants with relatively mild DR; for example, in RISE and RIDE, endophthalmitis occurred in 4 of 500 ranibizumab-treated patients (0.8%), from a total of 10 584 intravitreal injections over 2 years.[22] Careful follow-up and prompt initiation of panretinal laser and/or surgical intervention should remain the mainstay of treatment for eyes with advanced nonproliferative or frank proliferative disease until other specifically designed clinical trials compare outcomes of anti-VEGF therapy with PRP for proliferative disease; however, the effects on retinopathy severity demonstrated with ranibizumab in this study are substantial. If less invasive or extended-duration anti-VEGF treatments are developed in the future, their use primarily to control DR severity could be explored and potentially justified.

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