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The Clinical Importance of Changes in Diabetic Retinopathy Severity Score

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Purpose: To investigate the clinical importance of changes in diabetic retinopathy severity score (DRSS) in patients with diabetic macular edema (DME) treated with intravitreal ranibizumab.

Design: Post hoc analysis of the phase III RIDE and RISE studies of ranibizumab for treatment of DME.

Participants: Four hundred sixty-eight eyes treated with ranibizumab from randomization with gradable DRSS on baseline fundus photographs.

Methods: Visual and anatomic outcomes were examined in eyes grouped according to DRSS change from baseline to month 24.

Main Outcome Measures: Mean best-corrected visual acuity (BCVA) letter score change, proportion of patients with 15 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letter score change, mean contrast sensitivity change, proportion of patients with resolved macular edema, and leakage on fluorescein angiography.

Results: Most (56.8%) patients treated with ranibizumab experienced 1-step or more improvement in DRSS from baseline to month 24; 40.0% had no change, and 3.2% experienced DRSS worsening. Patients with DRSS stability or improvement had greater mean BCVA letter score changes (+15.1, +14.2, +11.3, and +11.2 letters for ≥3-step improvement, ≥2-step improvement, 1-step improvement, and no DRSS change, respectively) compared with +5.0 letters in patients who had any DRSS worsening. Best-corrected visual acuity letter score gain of 15 letters or more was more common in patients with 2-step or 3-step or more DRSS improvement (51.9% and 44.6%, respectively) compared with those with a 1-step DRSS improvement, no change, or worsening (37.9%, 39.6%, and 26.7%, respectively). A loss of 15 letters or more in BCVA was more common in patients with any DRSS worsening (13.3%) compared with patients who had stable or improved DRSS (0%−2.8%). Resolution of macular edema was more common in patients with DRSS improvement: 84.2%, 87.7%, and 92.3% of patients with 1-step, 2-step or more, and 3-step or more improvement in DRSS achieved central foveal thickness of 250 μm or less, compared with 65.2% and 53.3% of patients who had no DRSS change or any DRSS worsening.

Conclusions: These findings provide further support that improvement in DRSS is a clinically important outcome that should be evaluated as a measure of treatment effectiveness in future studies of diabetic eye disease. *Ophthalmology 2017;■:1−9 © 2017 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/).*

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The retinal findings that diabetic retinopathy (DR) comprises are defined by discrete steps of disease worsening using the Early Treatment Diabetic Retinopathy Study DR severity score (DRSS), which is evaluated commonly in clinical trials using color fundus stereophotographs evaluated by an independent reading center.[1] Simplified versions of this severity scale (for example, mild or severe nonproliferative DR) are used routinely in the clinic both to describe patient status and appropriate intervals for routine follow-up and to assess when interventions such as panretinal photocoagulation become necessary, such as when frank neovascularization occurs. With each advancing level of DR severity along this scale, the future risk of proliferative DR (PDR) developing and consequent vision loss increases.[2,3] Because of this correlation, a major goal and outcome measure of numerous trials for DR has been the prevention of DR severity worsening.

There are a number of systemic therapies and approaches that have been demonstrated to have beneficial effects on DR severity, as evidenced by reduced rates of DRSS worsening. Improvements in control of blood glucose[4,5] and systemic blood pressure[6] have been shown to be beneficial by a number of public health studies and form the core of metabolic control for diabetes, in large part because of their long-term benefit on reducing the rate of development or worsening of diabetic microvascular complications. Systemic medications such as candesartan, losartan, and fenofibrate also have shown promise,[7−9] but none of these drugs currently are approved or in widespread use as a primary means to either prevent DRSS worsening or to improve DRSS. Recently, 2 classes of intravitreal therapies have been shown to benefit DRSS: anti−vascular endothelial growth factor (VEGF) therapy and corticosteroids.[10−14]

The RIDE (clinicaltrials.gov identifier, NCT00473382) and RISE (clinicaltrials.gov identifier, NCT00473330) studies were 2 methodologically identical, phase III, double-masked, sham injection-controlled randomized clinical trials of ranibizumab for treatment of patients with diabetic

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macular edema (DME).[15,16] In a prior analysis of the RIDE/RISE cohort, it was shown that ranibizumab injections both reduced the risk of worsening and improved DRSS in a significant proportion of patients.[13] By month 24, 36.5% of eyes treated with ranibizumab had a 2-step or more DRSS improvement versus only 5.4% for eyes treated with sham injections. Analysis of the RIDE and RISE cohort also demonstrated that delayed ranibizumab therapy in the group of eyes that received sham injections for 2 years and then monthly ranibizumab until year 3 did not result in a similar extent of DRSS improvement as those eyes that were treated from baseline with ranibizumab.[14] Furthermore, an analysis of the RIDE and RISE cohort that entered an open-label extension with pro re nata re-treatment criteria from the end of year 3 to approximately year 5 showed that the DRSS improvement seems to be preserved over the long term with a minimum number of injections (fewer than 4 annualized injections in the open-label extension period).[17]

Anti-VEGF therapy frequently is used to treat DME,[18] but has not been used typically as a primary therapy to improve DR severity. Recently, the United States Food and Drug Administration approved 2 intravitreal anti-VEGF agents, ranibizumab and aflibercept, as treatments for DR severity in patients with DME.[19,20] The observations of the beneficial effect of ranibizumab on DR severity in DME patients, the need to treat early to maximize these improvements, and the stabilization of DRSS in the long term with a minimum need for re-treatment after DME has resolved suggest that further exploration of the clinical significance of changes in DRSS is warranted.

The relationship between improvement in DRSS and changes in both visual function and macular anatomic features has yet to be evaluated for clinical impact. In part, this is because a safe, reliable, and commonly used treatment to improve DR severity had not been available until the advent of anti-VEGF therapy. The cohort of eyes in RIDE and RISE trials, all of whom had visual loss resulting from DME at baseline, affords an opportunity to study the relationship between improvement in DRSS and changes in visual function (visual acuity and contrast sensitivity) and anatomic features (macular thickness as measured by optical coherence tomography [OCT] and leakage on fluorescein angiography [FA]) in eyes with DME treated with ranibizumab.

Methods

Study Design

Details of RIDE and RISE study methods have been reported previously.[15,16] In brief, adults with decreased vision resulting from DME (best-corrected visual acuity [BCVA] score, 20/40−20/320 Snellen equivalent) and macular edema (time-domain central subfield thickness, ≥275 μm) were randomized to receive monthly intravitreal injections of ranibizumab 0.3 mg or 0.5 mg or to receive monthly sham injections. The trials adhered to the tenets of the Declaration of Helsinki and complied with Health Insurance Portability and Accountability Act. Protocols were approved by institutional review boards or ethics committees as applicable. Patients provided written, informed consent. The primary efficacy outcome was the proportion of patients gaining 15 or more Early Treatment Diabetic Retinopathy Study visual acuity letters from baseline to month 24.[16]

The present subanalysis evaluated 24-month outcomes from patients who had gradable fundus photographs (n = 468). As previously reported, most ranibizumab-treated patients showed DRSS improvement, whereas most sham-treated patients showed no change in DRSS at month 24; as such, data from the sham-treated groups were not included in the present analysis of DRSS improvement. Data from the ranibizumab 0.3-mg and 0.5-mg groups were combined because BCVA score, OCT results, and DRSS outcomes were similar between the 2 dose groups.[13−16]

Visual and Anatomic Assessments

The change in DRSS from baseline to month 24 was determined from evaluation of color photographs at the University of Wisconsin Fundus Photograph Reading Center. Visual function assessments included changes in BCVA letter score (assessed by Early Treatment Diabetic Retinopathy Study visual acuity testing), the proportion of patients with a BCVA letter score improvement of 15 letters or more, or a BCVA letter score worsening of 15 letters or more. Change in contrast sensitivity was measured from baseline to month 24 using the Pelli-Robson chart.[21] The proportion of patients who had resolution of baseline macular edema at month 24 (central foveal thickness, ≤250 μm) was assessed by time-domain OCT. Leakage on FA was evaluated for area of leakage by the University of Wisconsin Fundus Photograph Reading Center. Visual function and anatomic outcomes were examined in patients grouped according to the level of change in DRSS from baseline to month 24: any DRSS improvement, any DRSS worsening, no change, 1-step improvement, 2-step improvement, and 3-step or more improvement.

Results

Baseline DRSS results for the 468 patients included in the present analysis have been published previously[13] and are shown in Table S1 (available at www.aaojournal.org). Most patients (60.3%) had nonproliferative DR (mild, moderate, or moderately severe) or mild PDR (28.4%). Because patients with clinically active retinal neovascularization were excluded from the RIDE and RISE studies, the patients with PDR at baseline in general were patients who had previously undergone panretinal photocoagulation (in whom the DRSS is level 60 by definition and the DRSS level in these eyes, by definition, could not improve).

Most ranibizumab-treated patients (56.8%) experienced at least a 1-step improvement in DRSS from baseline to month 24 (Fig 1), whereas a worsening in DRSS was observed in just 3.2% of these patients. The remaining 40.0% remained stable and experienced no change in DRSS level from baseline to month 24. Change in DRSS at month 24 by baseline DRSS is shown in Table S1 (available at www.aaojournal.org).

Among patients with any DRSS improvement, there was a trend toward greater improvement in mean BCVA letter score (Fig 2) as compared with patients who experienced DRSS worsening. Patients with a 2-step or 3-step or more DRSS improvement had mean BCVA letter score improvements of +14.2 and +15.1, respectively, whereas patients with any DRSS worsening had a lower mean BCVA letter score improvement of +5.0. A 3-line improvement in BCVA letter score (improvement of 15 letters or more) was also more common in patients with a 2-step or 3-step or more DRSS improvement